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July 1961

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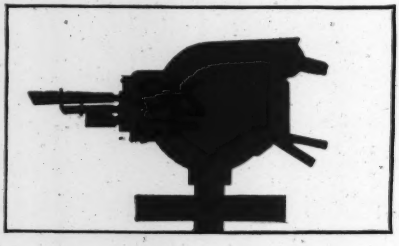

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CORRESPONDENCE

CONSULTANT welcomes questions and comments about any of the topics covered. The authors will answer all questions by mail, and some of the most informative replies will be published in this section, (names will be withheld on request). Please address all correspondence to CONSULTANT, SK&F Laboratories, 1500 Spring Garden Street, Philadelphia 1, Pa.

Articles on Orthopedics, Antibiotics

Gentlemen:

Have seen a copy of your first issue of CONSULTANT, and think it excellent. . . .

Just a suggestion: articles on orthopedics . . . would be helpful. Also latest preferences of antibiotics from authorities in the field would be appreciated. . . .

– D. J. Fellow, M.D.
Los Angeles, Calif.

By coincidence, an article on orthopedics appears in this issue; one on antibiotics is a possibility for a future issue. We appreciate receiving suggestions from readers and would like to hear from others who have ideas about articles for CONSULTANT.

Sinus Puncture

(Consultant, April '61)

Dear Doctor Seltzer:

You write of using "cocaine gel" prior to antrum puncture. Is this a commercial preparation? If not, how do you prepare it?

– E. V. Lewis, M.D.
Orange, California

The cocaine gel, which we also call cocaine "mud" for reasons that will be apparent to you if you mix it, is not a commercial preparation. It's easy to prepare, however, as follows: Place three or five gr. cocaine in a mixing jar and add 12-15 drops of 1:1000 adrenalin solution, then mix. The result will be a muddy-looking gel which can be applied to the point at which puncture will be made. Three or five gr. cocaine is needed because the adrenalin will shrink the tissues and restrict cocaine absorption somewhat. To be sure there is no sensitivity to cocaine, you can spray the nasal cavity lightly with 1% solution first and then wait about 15 minutes.

– Albert P. Seltzer, M.D.

Dumping Syndrome

(Consultant, May '61)

Dear Dr. Ferguson:

. . . After surgery for gastric cancer, what per cent of the patients can be expected to have the dumping syndrome, and what do you do about it?

– J. Montgomery Black, M.D.
Cleveland, Ohio

I don't know why, but the dumping syndrome is infrequent – almost rare – after gastrectomy for gastric cancer. This is in contrast to gastrectomy for gastric ulcer. Dumping or premature release of the contents of the stomach into the jejunum is caused by the decreased size of the stomach after resection and by the loss of the pyloric sphincter. When food does not remain in the stomach long enough to be diluted with gastric secretions, the dilution must take place in the jejunum. The required dilution is greatest with food containing salts and carbohydrates, especially sugars. The fluids required for dilution in the jejunum are drawn from the circulating blood. The resulting loss of blood volume, together with distension of the jejunum caused by too rapid release of food from the stomach, seems to be responsible for the symptoms we associate with the dumping syndrome.

With this mechanism in mind, the management of the disorder is fairly easy. Naturally, the patient is advised to avoid sugar, such as cake frosting and other sweets, and highly salted foods, such as meats and soups. Also the patient is advised to eat a dry meal because liquid foods tend to be more rapidly emptied from the stomach. I find that most patients quickly learn which foods cause dumping and, thereafter, get along very well.

– L. Kraeer Ferguson, M.D.

Alcohol, Tobacco, and Ulcers

(Consultant, May '61)

Dear Doctor Rider:

I read your interesting paper on "Duodenal Ulcer: Why Does Treatment Often Fail?". You didn't mention alcohol as an irritant. I advise all my patients to never drink or smoke again following a positive ulcer diagnosis. Please comment.

– Ernest G. Homokay, M.D.
Silver Creek, N. Y.

I have received your question concerning the abstinence from alcohol and smoking in anyone who has a positive ulcer diagnosis. As I mentioned in the article, I attempt to restrict or possibly discontinue the use of tobacco since it is in many instances a stimulant of gastric secretion. But as you well know, many patients refuse to follow this advice, so we have to compromise by having them reduce the number of cigarettes they smoke a day. Once the ulcer is healed and the patient is on a basic medical regimen, tobacco is probably not too important in producing an exacerbation of symptoms.

Alcohol is, of course, a potent stimulant of gastric acidity and must be stopped completely during the acute phase of the peptic ulcer. Once the ulcer is healed, it is usually permissible for a patient to have one highball or a small glass of wine just before eating as the food will effectively neutralize the increase in gastric acidity.

While these restrictions are desirable, they may not always be completely necessary. From a practical point of view, I have found it impossible to achieve patient cooperation to the extent that they will completely abstain from smoking or drinking for the rest of their lives.

– J. Alfred Rider, M.D.

Variations in Postnasal Packing

(Consultant, June '61)

Dear Doctor Seltzer:

I read your article in the June '61 CONSULTANT several times with great interest. However, I am at a loss to figure out the purpose of the third string on each posterior nasal packing. On the occasions I have had to use posterior nasal packings, I have used only two strings and found them quite sufficient.

– Albert R. Fritz, M.D.
Brooklyn, N. Y.

The third string, which is left protruding from the mouth and taped to the cheek, facilitates removal of the packing through the mouth. Postnasal packing is sometimes done without this extra string for removal, in which case the packing must be grasped with a curved hemostat and pulled out through the mouth. I prefer to use the third string, however, for convenience and as a safety measure. I remember a case in which no third string was used when the strings through the nostril of a 4-year-old became untied during the night and the packing dropped down into his throat and choked him.

– Albert P. Seltzer, M.D.

Persistent Nosebleed

(Consultant, June '61)

Sir:

What measures would Doctor Seltzer suggest to stop nosebleeds that are persistent and fairly profuse, but not really severe enough to warrant packing? I have in mind the sort of nosebleed that occurs in certain hypertensive patients.

– Henry V. Grahn, M.D.
Philadelphia, Pa.

The type of bleeding you describe usually originates in the plexus of small vessels at the lower end of the septum (Kiesselbach's-Little's area), so that it is accessible for control by applying pressure over the bleeding point. An ordinary, spring-controlled clothespin is a simple but effective means to apply pressure. Simply place, or have the patient place, a piece of gauze over the nose and apply the clothespin over the gauze, leaving it in place for about 20 minutes to stop the bleeding. I always make it a point to carry a couple of spring clothespins with me. When the bleeding point can't be reached to apply pressure, an injection of 1% procaine and 1:50,000 adrenalin will sometimes stop the bleeding; if not, it prepares the area for cauterization. A word of caution: You will, of course, be treating the underlying condition which causes epistaxis, but at the same time should be on the lookout for development of anemia. This sometimes develops with persistent nosebleeds, even though they seem mild and easy to control.

– Albert P. Seltzer, M.D.

When Patients Shouldn't Drive

(Consultant, June '61)

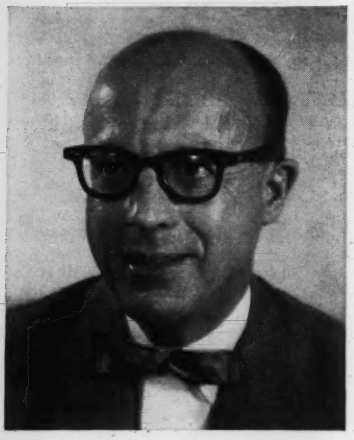
Sir:

Please send complete chart listing all conditions which may make a person ineligible to drive. The chart mentioned on page 45 of June 1961 CONSULTANT. Incidentally, your magazine is excellent.

– E. E. Baden, M.D.
Raymondville, Texas

A copy of the chart has been sent to Doctor Baden. Other readers who may have missed the June issue can still obtain copies of the chart, listing conditions which may make persons ineligible to drive personal or commercial vehicles, by writing to: CONSULTANT, SK&F Laboratories, 1500 Spring Garden Street, Philadelphia 1, Pa.

ENDOCRINOLOGY



Herbert S. Kupperman, M.D.
New York University

Herbert S. Kupperman is Associate Professor of Medicine at New York University Postgraduate Medical School, Associate Visiting Endocrinologist at Bellevue Hospital, and consultant in endocrinology for 15 other hospitals in the New York area. He is a member of the editorial boards of the JOURNAL OF CLINICAL PHARMACOLOGY AND THERAPEUTICS, and the JOURNAL OF CLINICAL ENDOCRINOLOGY AND METABOLISM, and the author of 46 articles on various aspects of endocrinology.

HYPOGONADISM IN BOYS: THE CASE AGAINST "WATCHFUL WAITING"

Every physician must, now and then, decide what to do about hypogonadism in boys – leave it untreated and wait for spontaneous puberty, or institute hormonal therapy? I am convinced that the prevalent conservative policy of "watchful waiting" is unwise; too often it means, in effect, "Do nothing until it's too late." Instead, a policy of judicious early treatment is recommended.

Let me tell you about one of the patients whose history led me to this admittedly controversial position.

Patient S. K. came to me for treatment at age 32. He had sought treatment elsewhere during adolescence but had been refused hormonal therapy. He was short and markedly un-masculine in appearance; he had infantile genitalia, and secondary sex characteristics were totally absent. Bone X-rays showed that his epiphyses were long closed–an indication that treatment would be futile. Nevertheless, intensive hormonal treatment was undertaken. Unfortunately, massive doses failed to stimulate penile growth or alter his appearance. He will live his life as a eunuch.

This is an extreme example, but such cases are not so rare as this one sounds. Actually results can be disappointing in far younger patients. The rule is: the younger the patient, the more responsive he will be to treatment. As he gets older, his capacity for response to gonadotropic hormone grows progressively less until the epiphyses are closed and hypogonadism is irreversible.

Another important reason for early treatment is to foster normal psychosexual development. The psychological effects of delayed genital development are particularly severe. The growing boy with an infantile penis may be ridiculed by his associates, especially among any group of children or adolescents using common bathing facilities. As a result, he may become self-conscious and anxious to the point of abnormal behavior.

Clearly, early treatment is desirable and necessary. But, how to recognize the patient who will respond, how to choose the appropriate method, and when to begin? The first and most important step, of course, is careful physical examination to determine whether or not hypogonadism is truly present by comparing genital size and body development with that of normal boys of the same age and build. *Remember, hormonal therapy is not advocated except for the patently abnormal child.* If the boy's penis is normally small, or perhaps only looks small because of obesity, it is important to stress this fact to the parents, lest they *create* a problem.

Next is careful endocrine appraisal—including an evaluation of testicular and pituitary function, and possible thyroid and adrenal factors; it is necessary to distinguish between delayed puberty, testicular insufficiency, and gonadotropic insufficiency.

Because hypothyroidism is a common cause of secondary hypogonadism, diagnostic studies should begin with thorough appraisal of thyroid function via serum PBI, cholesterol, photomotogram, and glucose tolerance tests; in addition, a roentgenographic (not fluoroscopic) evaluation of bone age for signs of retardation provides an important clue to thyroid function. Clinical findings which suggest hypothyroidism include: dryness of the skin, particularly on the extensor surfaces of the body; tendency toward dryness of the scalp and toward constipation; increase of lanugo-like hair on the dorsal areas; intolerance to cold; and general sluggishness of thought and action.

Once hypothyroidism has been ruled out, you must determine the activity of the pituitary-gonadal system. First, the physical signs: hypoplastic genitalia and failure to develop secondary sex hair are characteristic. Laboratory confirmation of pituitary-gonadal deficiency is obtained by the determination of 17-ketosteroid excretion. This is an index in part of the amount of gonadal hormone secreted by the testes. Normally, the excretion of 17-ketosteroids is approximately 0.5-1.0 mg. per 24 hours per year of life (the normal range for the adult male is between 10 and 24 mg. per 24 hours). If the excretion rate is low, with or without retarded bone age, and the gonads are hypoplastic, the patient is a candidate for gonadal-stimulation therapy.

When To Begin Therapy

What *is* the appropriate age at which to begin hormonal therapy? Is it 8, 10, 14, or 18 years—or even 30 years in adults? How long should one wait for spontaneous puberty before beginning therapy? I believe that one should not wait at all but should begin treatment as soon as primary hypogonadism is diagnosed. If endocrine treatment is delayed until the age of 18, 20, or 30 years, there may be a poor response or no response at all.

Watchful waiting is no more indicated here than it is for a broken arm.

Those who argue for "watchful waiting" base their position on fear of side effects—mainly of premature epiphyseal closure with resultant curbing of normal growth. Our experience does not justify these fears. We are convinced that acceleration of penile and testicular development with gonadotropic hormone has no adverse effects on the patient's future height or function. Such effects are possible with androgenic steroids; however, the latter are already contraindicated in primary hypogonadism.

A Suggested Treatment Program

Once the decision for treatment is made, here is the approach I find most effective.

In Patients Under 9 Years...

500 i.u. of human chorionic gonadotropin, I.M., three times a week for 3 weeks; then twice a week for 3 weeks; in addition, an anabolic steroid, such as norethandrelone, should be given orally, 10 mg./day or every second day. This steroid is added because of the synergistic effect it has with chorionic gonadotropin in enhancing the patient's growth response where desired.

In Patients Over 9 Years...

1,000 i.u., I.M., 3 times a week for 3 weeks; then twice a week for 3 weeks; in addition, norethandrelone should be given 10 mg. b.i.d. for 3 weeks, and u.i.d. thereafter.

The above dosage schedule is based on average cases; it may need altering according to the patient's size and body build, and the degree of hypogonadism present. For example, an unusually large 8-year-old boy might need the dosage advised for a 10-year-old; a small, asthenic, 11-year-old with mild hypogonadism might respond well to the dose recommended for 8-year-olds.

Eight weeks after initiation of treatment, the patient's response is evaluated. Usually, a single course of therapy is enough. However, if further improvement is desirable, a second course of therapy may be begun a month or two later. Failure to respond to chorionic gonadotropin is rare and, in the young patient, indicates primary testicular failure or aplasia. Such a patient requires continuous replacement therapy with androgenic steroids—but this is another subject, beyond the scope of this article.

The described method of therapy will produce, in addition to the increase in the size of the genitalia, a beginning development of pubic and axillary hair. These are not undesirable manifestations of the patient's response to an increased production of endogenous steroids. Bilateral gynecomastia, with or without tenderness, may also develop after the use of chorionic gonadotropin in the preadolescent hypogonadal male. This is an undesirable side effect that will usually subside when therapy is discontinued.

In summary, then, I believe the philosophy of watchful waiting is hazardous and should be replaced with a policy of judicious early use of gonadotropic therapy whenever primary hypogonadism is present. Early therapy will prevent permanent sexual infantilism and aid normal psychosexual development. Predicted undesirable effects of hormonal therapy are more myth than fact and do not justify the hazards inherent in delay.

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1. Lemere, F.: Tranylcypromine ('Parnate'), A New Monoamine Oxidase Inhibitor, Am. J. Psychiat. *117*:249 (Sept.) 1960.
2. Petersen, M.C.: Depression: Treatment with a New Antidepressant—Tranylcypromine, report accompanying scientific exhibit at the 116th A.P.A. Meeting, Atlantic City, New Jersey, May 9-13, 1960.
3. Roebuck, B.E., and Maccubbin, H.P.: Treatment of Depression with Tranylcypromine, report accompanying scientific exhibit at the 13th Annual A.M.A. Clinical Meeting, Dallas, Texas, Dec. 1-4, 1959.

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PEDIATRICS

Robert B. Lawson, M.D.
University of Miami

Robert B. Lawson is Chairman of the Department of Pediatrics at the University of Miami School of Medicine, and Pediatrician-in-Chief at Jackson Memorial Hospital. In 1940-1942 he was pediatric consultant to the North Carolina State Board of Health, and one of his major interests was conducting postgraduate courses in pediatrics for general practitioners. After this appointment, he organized and directed the Department of Pediatrics of the newly enlarged Bowman Gray School of Medicine. He is the author of 35 published articles on various aspects of pediatrics; in addition, he has served as Chief Editor of the A.M.A. JOURNAL OF DISEASES OF CHILDREN.

THE ART OF INTELLIGENT NEGLECT

Do we physicians have to give some form of treatment to every child brought to us? Should we prescribe a medicine just because the family expects it? Most of us would readily answer, "Of course not." And yet, because of our training to relieve illness, it is sometimes difficult to resist pressures to "do something" for our patients. Moreover, there are certain conditions in children that are difficult to assess for need of treatment. Let us look at some of these "borderline" conditions where, more often than not, treatment is really not necessary and, in fact, may do more harm than good.

Developmental Variations

Failure to recognize self-limited variations from normal sometimes leads to unnecessary treatment. The "normal" child shows a wide variation in weight, height, and in reaching the landmarks of physical and mental development. Generally, infants tend to lose their fat, baby-like appearance during the second year of life, and at the same time develop day-to-day swings in appetite. This worries parents because they tend to equate *bigness* both in appetite and weight with good *health* (an attitude, incidentally, that may well lead to obesity in later childhood as the child unconsciously seeks to gain approval by overeating). The parents' overemphasis on food will only be exaggerated further by a prescription for vitamins and tonics to stimulate the appetite. Here is a classic example of a normal process—temporary reduction in food intake—being treated unnecessarily. Instead of being reassured by the doctor's concern, the parents believe that the

child's loss of appetite is important. Further, when the treatment with vitamins and tonics does not produce the desired increase in appetite, the parents may lose confidence in the doctor. When faced with an appetite problem in a healthy child, it is much better to take a few minutes to explain that variations are to be expected; showing the child's position on the percentile tables should reassure parents that the child is, in fact, well and needs no medication.

Minor defects and variations in development only rarely need treatment, and then only with specific indications. *Umbilical hernia,* even though large, will correct itself without strapping. *Capillary hemangioma,* or port-wine stain, neither goes away nor is satisfactorily treated by any means. *Raised hemangiomas* or strawberry marks will disappear if left alone, and the eventual appearance of the skin is as good as or better than that achieved by treatment which, injudiciously applied, may cause scarring. These lesions usually appear at birth or shortly afterwards, and increase until 7 to 10 months of age. Gradual fading then begins in the center, and the lesions usually disappear by 3 to 5 years of age. Many unnecessary *tonsillectomies* are done merely because the tonsils are large; size alone is a poor criterion. *Physiologic flat feet, bowlegs,* and *knock-knees* in the first 5 years are needlessly treated conditions which are usually completely corrected by the beneficial progress of normal growth. *Tongue-tie* does not create difficulty in nursing and has little if any effect on speech, never causing delay; clipping is indicated only in exceptional cases. *Upper labial frenum* does not cause separation of the incisors and is almost always corrected by eruption of the permanent teeth; surgical removal may leave scar tissue which can make later orthodontic correction, if necessary, more difficult. In all these conditions, reassurance and unobtrusive watching will produce a better end-result than ill-advised treatment.

Viral Infections

Viral infections of the respiratory and gastrointestinal tracts are too often treated with antibiotics. Although these drugs have no antiviral action, the tendency is to use them anyway, either because of fear of missing a bacterial infection, or in order to prevent a complicating bacterial invasion —in spite of the fact that prophylactic therapy has no proven value. It is true that differentiating between viral and bacterial infections is difficult; however, it is not impossible if we consider the clinical picture and the local epidemiologic pattern. When in doubt, we may feel forced to treat, but in doing so should explain why the child is being treated so that undue faith is not built up in antibiotics for viral infections. The excuse that the family demands a shot or a "mycin" does not justify the unwarranted use of potentially harmful and costly drugs.

Problems Of Over-Solicitude And Over-Protection

Finally there are situations in which a definite disorder has been diagnosed and probably needs treatment but must be kept in perspective and not exaggerated in importance. A common example in children is the innocent heart murmur. When detected, it should be mentioned to the family but must not be left as a threat to the child. Its innocence must be empha-

sized, and no restrictions on the child's activities must be allowed. All too often a physician leaves a family in limbo when he says, "We will watch him, but don't let him overdo!" Even if it were an organic murmur, there would be no harm in full activity in the absence of cardiac enlargement or functional impairment. A similar situation follows a diagnosis of rheumatic fever, diabetes, or asthma. Although specific therapy and follow-up prophylaxis are necessary, it is important that as much freedom as possible be allowed in the child's activity so that feelings of inadequacy do not lead to chronic invalidism. Undue restrictions lead only to over-solicitude and overprotection.

I am saying, in other words, that normal concern and alert observation of a child lead to good preventive measures and healthy guidance, but that over-concern leads to over-treatment. I am not preaching therapeutic nihilism but am urging physicians to recognize those situations where restraint is indicated. There are three such situations: when the treatment may prove more harmful than the disorder itself; when failure to recognize self-limited variations from the normal may lead to insecurity on the part of the parents; and when undue emphasis on treatment may exaggerate the problem it is meant to control.

I know the pressure to "do something" is always there—but often the test of good medicine is to practice the art of intelligent, planned neglect rather than to treat when treatment is not necessary.

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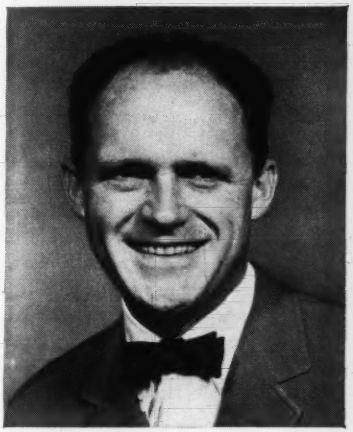
GYNECOLOGY



James A. Merrill, M.D.
University of Oklahoma

James A. Merrill was recently appointed Professor and Head of Gynecology and Obstetrics at the University of Oklahoma School of Medicine. He is a graduate of the University of California School of Medicine and a diplomate of the American Board of Obstetrics and Gynecology. Dr. Merrill is a member of the Society for Gynecologic Investigation and the Inter-Society Cytologic Council. In 1957, he was one of 25 American medical scientists to receive a Markle Scholarship to continue his studies in gynecologic pathology and pelvic malignancy, his major interests.

ENDOMETRIAL HYPERPLASIA

Endometrial hyperplasia is a frequent cause of excessive and prolonged menstruation in patients at the two extremes of menstrual life – the teenage, post-pubertal girl and the mature woman approaching the menopause. Despite the difference in age, the underlying pathologic physiology is usually the same – continued, unopposed estrogen activity resulting from prolonged anovulation. Estrogen activity need not be excessive to produce endometrial hyperplasia if it is prolonged and unopposed by progesterone from a corpus luteum. However, it occasionally may result from excessive estrogen – either endogenous (ovarian tumors or polycystic ovarian disease) or exogenous. In fact, endometrial hyperplasia may be associated with a variety of endocrine disorders which sometimes require complex therapy, but a discussion of these disorders is beyond the scope of this article.

The Post-Pubertal Patient

In the case of the teen-ager who complains of irregular, excessive, or prolonged menstruation shortly following the menarche, endometrial hyperplasia is the most common cause and, therefore in my opinion, may be diagnosed without resorting to dilatation and curettage of the uterus, or even endometrial biopsy. Certainly this is so if a careful pelvic examination reveals no abnormalities and the remainder of the general physical examination is normal.

Since anovulation exists, estrogen is present in adequate or even excessive amounts; therefore, treatment should consist of the cyclic administration of

progesterone without estrogen. My preference is progesterone-in-oil given as a *single* deep intramuscular dose of 50 mg. at *exactly* 4-week intervals. Menstrual bleeding, usually neither excessive nor prolonged, follows the injection within 3-7 days. Or 100 mg. of progesterone-in-oil may be given (as a medical curettage) for initial control of a prolonged bleeding episode. When using progesterone for immediate hemostasis, warn the patient that bleeding may stop within a day or so but will resume again in about three to four days and then be self-limiting. Unnecessary polyhormonal therapy has often been used simply because of a lack of understanding of the action of progesterone.

After treatment for two or three cycles of four weeks, lengthen the interval between medication to five weeks. This is one way to avoid unnecessary progesterone administration by allowing spontaneous menses if your patient begins to ovulate. Actually, a better way would be to detect ovulation before injection, by asking your patient to keep a basal body temperature graph, but, in my experience, most youngsters are not very dependable keepers of graphs. Discontinue cyclic therapy when ovulation occurs or after approximately six months if anovulation persists.

In addition to progesterone, iron therapy should be given if your patient is anemic. A vitamin complex rich in thiamine may be added, but rarely will any other drugs be necessary. Successful management depends upon the *regular*, cyclic administration of progesterone without other hormones, especially complex, multiple, or long-acting hormonal preparations.

The Premenopausal Patient

The management of endometrial hyperplasia in women approaching menopause will be somewhat different, because diagnosis can be made only by pathological examination of endometrial curettings. Moreover, dilatation and curettage of the uterus is indicated for all women in their forties with a complaint of excessive or prolonged menstruation. The procedure is of both diagnostic and therapeutic value; it is especially valuable for excluding endometrial carcinoma. Moreover, a more thorough pelvic examination may be done to exclude the rare associated ovarian neoplasm. Endometrial biopsy in the office is of value if carcinoma is found, but it is not a reliable means of assuring the benign nature of an endometrial abnormality.

There is good evidence to suggest that endometrial carcinoma is preceded, in many cases, by endometrial hyperplasia, and the pathologic criteria for diagnosing these premalignant lesions are now fairly well established. Therefore, if the pathologist describes the curettings as endometrial hyperplasia, predominantly adenomatous with atypical or anaplastic changes, the curettage should be repeated in three months. Sometimes the process shows evidence of regression following this period ot observation. However, if it shows evidence of progression, abdominal hysterectomy should be strongly considered, especially for the postmenopausal patient. Not a few such patients have an associated estrogen-producing lesion of the ovary.

When treating the menopausal woman for hyperplasia, be certain she is not receiving estrogen from another phy-

sician, or from careless refilling of an old prescription, or, as occasionally happens, from cosmetics containing estrogen. (Ask her specifically about this last possibility.) Indeed, exogenous estrogen may even produce adenomatous, atypical hyperplasia, which will be reversed completely when the estrogen source is removed.

When the premalignant process is absent or, if present, regresses during the period of observation, medication may be necessary for symptomatic relief. Remember, however, that about 75% of women are cured of their bleeding abnormalities following dilatation and curettage of the uterus. If they are not, progesterone may be given in precisely the same manner as described for teenage girls. Of course, the return of cyclic ovulation is not to be expected in menopausal women; therefore, administration of the hormone can be continued regularly at 4-week intervals until the patient shows evidence of spontaneous cessation of menstruation.

If progesterone is not effective (and occasionally it is not), methyltestosterone may be used to good advantage. Begin with a 10 mg. buccal tablet daily for the first 25 days of the cycle. Thereafter, reduce the dose to 5 mg. daily and continue treatment until menses cease. During the continuous administration of methyltestosterone, menstruation of normal or less than normal amounts will occur at somewhat irregular intervals, which gradually lengthen until finally menses cease.

I do not mean to imply that the treatment recommended here is universally successful, nor can repeated curettage or more drastic surgical measures always be avoided. However, in my experience, the methods described have proven satisfactory in the great majority of women. Changes in hormone administration or further surgery have been seldom necessary. New hormonal medications and combinations of hormones continue to be developed, but, in my opinion, the simplest treatment remains the most efficient.

QUESTIONS AND ANSWERS

Q. *Can oral medication be substituted for the intramuscular injections that you recommended?*

A. Yes, if you prefer an oral medication, perfectly adequate results can be obtained by administering one of the new 19-norsteroids with progestational activity. For example, 10 mg. of Norlutin® or Enovid® twice daily for 3-4 days every four weeks.

Q. *You say that in the treatment of young girls, progesterone should be discontinued after 6 months even if anovulation persists. What should then be done if bleeding continues?*

A. The patient should be re-evaluated from the standpoint of a polyglandular endocrine abnormality. Adrenal studies may be in order as well as hematologic evaluation. Although curettage is used rarely in adolescent girls, a curettage may be necessary to exclude local lesions, if bleeding persists.

BREAKS THE HABIT OF COMPULSIVE OVEREATING

'Eskatrol' *Spansule* capsules provide daylong control of appetite *and* relief of the psychic stress that causes overeating. Because the tranquilizer component of 'Eskatrol' controls emotional stress, your patient has a better chance of staying on his diet —even for prolonged periods of time.

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Prescribing Information

FORMULA: Each 'Eskatrol' *Spansule* sustained release capsule contains Dexedrine® (brand of dextro amphetamine sulfate), 15 mg., and Compazine® (brand of prochlorperazine), 7.5 mg., as the dimaleate, distributed among hundreds of minute pellets with varying disintegration times. A therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours.

IN OVERWEIGHT PATIENTS: 'Eskatrol' *Spansule* capsules are indicated in overweight patients, particularly in those who depend on eating for psychologic release.

'Eskatrol' *Spansule* capsules provide not only daylong control of appetite but also relief from the emotional stress associated with overeating and with dieting. The desire to eat is reduced and patients, particularly the so-called "compulsive eaters," feel better and are able to adjust to the weight-reducing program—*even for prolonged periods of time.*

RECOMMENDED DOSAGE: One 'Eskatrol' *Spansule* capsule daily, taken in the morning.

SIDE EFFECTS: Side effects (chiefly nervousness and insomnia) are infrequent, and usually mild and transitory.

CAUTIONS: Clinical experience has demonstrated that 'Eskatrol' (containing the phenothiazine derivative, 'Compazine') has a wide margin of safety and that there is little likelihood of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence.

'Eskatrol' *Spansule* capsules should be used with caution in the presence of severe hypertension, advanced cardiovascular disease, or extreme excitability.

Adopted Jan. 1961

AVAILABLE: In bottles of 30 and 250 capsules.

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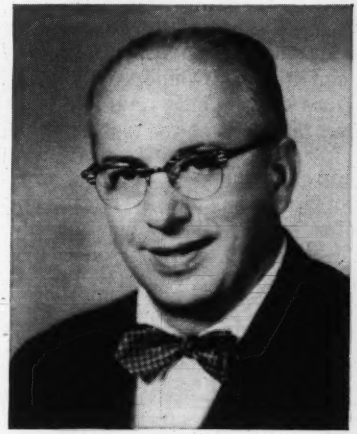
OTOLOGY



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PUZZLING EAR NOISES

Ear noise—tinnitus—is a great nuisance to the patient who has it and a great puzzle to the physician who has to treat it. Sometimes it may be heard in only one ear, or in both simultaneously, or first in one ear and later in the other. Some patients say their ear noises sound like the escape of steam, the blowing of a whistle, or the ringing of a high-pitched bell. Others compare the noises to running water or describe them as a roaring, buzzing, or hammering sensation. Occasionally the noise is in the head without reference to the ears, and it may be so loud that even the physician can hear it.

One young man complained of a distracting gurgle that seemed to indicate fluid in the middle ear. The patient was in excellent health, tanned and fit, and had no history of allergy or any sign of upper respiratory infection that could account for the symptom. He had been practicing skin diving, and, as he worked his way to greater depths, the pressure produced this fairly common skin divers' complaint. I inflated the eustachian tube to relieve the patient's ear noises.

Ear Disorders That Cause Ear Noises

Ear noise may be encountered in any form of ear disease. It takes place in nerve deafness, otosclerosis, Meniere's disease, and obstruction of the eustachian tube, to name a few of the more important ones. In cases of otitis media, pulsating noises are frequently produced. And, just as pain signifies irritation of a sensory nerve, ear noise may signify irritation of the cochlear mechanism.

Ear noise often results from the pressure of cerumen against the drum

membrane. Water entering the ear canal and causing dried cerumen to swell is a common occurrence, especially during the summertime when swimming is popular. Removing the cerumen with a cerumen spoon or syringing the ear with lukewarm water will bring relief. It may be necessary at times to first soften the cerumen with liquid albolene.

A gurgling noise in the ear is caused by fluid in the middle ear cavity and usually follows infection or allergy in the nose, sinuses, throat, or the ear itself. When the middle ear cavity is filled with fluid, it may be necessary to incise the eardrum to induce drainage.

Other Possible Causes

Ear noise is also a symptom of a number of general diseases that indirectly affect the ear through the circulation, as do hypertensive cardiovascular disease and various forms of anemia. It can come, too, from drugs such as quinine and the salicylates, as well as from the excessive and prolonged use of tobacco and alcohol, or, theoretically, from any substance to which the nerve tissue of the auditory mechanism is sensitive. Working under stress may account for a temporary siege of ear noises, especially in tense, emotional, high-strung individuals besieged by worries, anxieties, and overwork. The noises usually cease when the stress slackens. Finally, head injuries, intracranial tumors, and some diseases of the central nervous system that involve the auditory nerve are additional contributing factors.

Determining The Cause

The effective treatment of ear noise lies, of course, in the removal or treatment of its cause. However, from this brief consideration one can see that it is a symptom of a large number of clinical entities, not all of them related to the auditory apparatus by any means. So it is especially important to examine closely the occasions, events, and conditions surrounding the noise for clues to the cause and guides to proper treatment.

Recently I examined a young high school girl who awoke one morning to find her ear canals itching intensely and her lips and cheeks swollen. She was particularly distressed by the onset of ear noises. The finger of suspicion quickly turned to a dish of sea food that she had eaten the night before. Antihistamines gave prompt relief, and now she excludes oysters, lobsters, and shrimps from her diet.

While looking for clues that will lead to effective treatment, the physician has got to maintain the impression that he understands the seriousness of the annoyance and that he is doing everything possible to help. He must, in other words, try to provide symptomatic relief while looking for the cause.

Not so long ago a tense, high-strung businessman came to me complaining of ear noises that occurred every time he contracted some of the muscles around the ear, face, and jaw. When he was working under pressure, the ear noises intensified, but, as soon as the pressure lessened, they stopped. When the patient was assured that the ear noises were the result of anxiety and muscle contractions, he felt greatly relieved that his troubles were not permanent.

What Drugs Are Helpful?

There are many drugs that provide some symptomatic relief to some patients. None has been universally sat-

isfactory, yet each has done some good, and the same can be said for various surgical procedures. Among the drugs that have been found to provide relief occasionally are ephedrine, antihistamines, atropine, calcium, and large oral doses of Vitamin B. Iodides and various endocrine preparations are sometimes useful, and so are vasodilators, like nicotinic acid. Histamine desensitization seems to help some patients who show a positive response to histamine skin tests. But barbiturates and tranquilizers do the most good symptomatically, especially when administered at night, for ear noise is most disquieting in peaceful surroundings.

Distraction Sometimes Helps

Ear noise usually responds to removal of the underlying cause or to symptomatic treatment, or else it stops spontaneously. However, it sometimes does not. When that happens, preoccupation with some absorbing interest or hobby often provides an antidote. Before bedtime, background music supplied by a radio through earphones may eliminate ear noises from consciousness before the victim falls asleep. The most satisfactory clinical responses are obtained by convincing the patient that everything possible is being done for him, while encouraging him to ignore the ear noises as much as possible.

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OTHER INDICATIONS: 'Edrisal' affords unusually effective relief in such commonly encountered conditions as: chronic headache; low back pain; neuritis; neuralgia; arthritic pain, rheumatism and allied conditions; muscle and joint discomfort; sinusitis; phlebitis; certain cases of migraine.

FORMULA: Each tablet contains Benzedrine® Sulfate (brand of amphetamine sulfate), 2.5 mg.; aspirin, 2½ gr. (0.16 Gm.); phenacetin, 2½ gr. (0.16 Gm.). Unlike most analgesic preparations, 'Edrisal' is available on prescription only.

ADMINISTRATION: Two tablets every three hours if needed. Only in exceptional cases will more than six to eight tablets be required in a 24-hour period. For best results, 'Edrisal' should be given about half an hour before eating. In dysmenorrhea, best results are obtained by starting medication two days before menstruation.

In higher dosage ranges, certain individuals may experience some disturbance of sleep if 'Edrisal' is administered in the late afternoon or evening. This, however, can easily be controlled with a mild sedative.

SIDE EFFECTS: Instances of insomnia, excitability and increased motor activity—when they occur—are ordinarily mild, and can be controlled by adjustment of dosage.

CAUTIONS: Use with caution in patients hypersensitive to sympathomimetic compounds; in cases of coronary or cardiovascular disease; and in the presence of severe hypertension.

CONTRAINDICATIONS: Hyperexcitability; agitated pre-psychotic states.

AVAILABLE: In bottles of 50 and 500 tablets.

Prescribing Information adopted January, 1961.

INTERNAL MEDICINE

Benjamin Calesnick, M.D.
Hahnemann Medical College

Benjamin Calesnick is Assistant Professor of Pharmacology and Director of the Laboratory of Human Pharmacology at Hahnemann Medical College and also Chief of the Hypertension Clinic at St. Joseph's Hospital in Philadelphia. He is the author of 35 publications, mainly on the pharmacology of diuretics, analgesics, antihypertensive drugs, and radioisotope agents. His professional affiliations include the American Society for Pharmacology and Experimental Therapeutics, and the Society of Nuclear Medicine.

WHICH HYPERTENSIVE PATIENTS NEED TREATMENT?

Technically, a blood pressure above 160/90 mm. Hg is considered abnormal. Yet the question is often asked, "Which patients should be actively treated?" According to my experience, there are 3 groups that must receive antihypertensive therapy because of poor prognosis if left untreated: 1) men with diastolic hypertension, 2) patients with benign hypertension with familial history of malignant hypertension, and 3) all patients with malignant hypertension. I think the best way to describe these patients and their appropriate therapy is to relate three case histories, each one representing one of these three groups. Before doing that, however, I would like to put down some obvious but sometimes overlooked facts.

First, the essential parts of an examination to determine the severity of hypertension: familial and personal medical history, fundoscopic examination, chest X-ray, urinalysis, and blood urea nitrogen. For a reliable base line, repeated blood pressures should be recorded by the same person, at the same time of day, using the same equipment, on the same arm; and the examination should be done in an atmosphere of serenity and routine to avoid any emotional effect on blood pressure stemming from the procedure itself.

1. Men With Diastolic Hypertension

A 54-year-old laborer was admitted to the hospital complaining of severe occipital headache. For several years, he had noticed increasing dyspnea, and during the last 6 months had noticed daily swelling of the ankles. He did

not have precordial pain. At examination, his blood pressure was 175/110 sitting and 186/114 recumbent. His heart was enlarged to the left as far as the anterior axillary line. He showed a 2+ ankle edema and weighed 186 lbs. Laboratory tests showed a trace of albuminuria, specific gravity 1.018 (24-hour urine), normal CBC, and BUN 15 mg.%. The EKG showed a pattern of left ventricular hypertrophy confirmed by X-ray.

We began treatment with hydrochlorothiazide (50 mg. daily) and hydralazine (50 mg. t.i.d.). After 4 days, the blood pressure readings were down 20 points systolic and 14 diastolic. The patient now weighed 182 lbs. He no longer complained of headache, but did complain of feeling more tired. So we reduced the hydrochlorothiazide to 25 mg./day and supplemented his diet with 8 oz. of apricot juice daily. Within 48 hours, his fatigue subsided, but his blood pressure was unchanged. To reduce it further, we increased the hydralazine to 50 mg. q.i.d. One week later, his blood pressure was satisfactory at 146/92 sitting and 154/96 recumbent, and he was discharged on this regimen. Two weeks later, he was still comfortable. He weighed 180 lbs. and retained his previous reduction in blood pressure. He had only slight, pitting edema of the ankles, and the dyspnea, even at work, was markedly improved. He was considered stabilized at this point and was discharged for one month on the same regimen without limitation of salt intake. At the next examination he was, and still remains, well controlled and without gross complaints.

Comment

This is a classic case in terms of symptoms and physical and laboratory findings. It shows, too, that this kind of hypertension is readily controlled with a diuretic-antihypertensive combination. The occurrence of fatigue as a side effect and the varying response to different dosage levels of the drugs points up the need to adjust dosage carefully and individually in each patient.

2. Benign Hypertension With A Family History Of Hypertension

A 37-year-old salesman was admitted to the hospital for cardiovascular evaluation. He had recently been denied life insurance because of familial hypertension: his father died of a stroke at 35 and his brother of coronary occlusion at 46. Sitting blood pressures recorded by the insurance medical examiner ranged between 168 to 185 systolic and 110 to 118 diastolic. His medical history was negative, except for the usual childhood diseases.

For the first 4 days, he was under continuous observation without antihypertensive medication. During this time, the recumbent blood pressure readings ranged between 118 to 132 (systolic) and 76 to 84 (diastolic). Pulse rate ran between 82 and 94. He weighed 156 lbs., and all laboratory tests including EKG, chest X-ray, and the histamine provocative test for pheochromocytoma were in the normal range.

We decided to discharge the patient on reserpine (0.25 mg. t.i.d.) and told him to return for an examination after one week. He returned complaining of severe nasal stuffiness and slight nausea. Blood pressure had risen 20 points above the maximum previously

recorded. We then reduced the dosage to one tablet a day (0.25 mg.). The side effects still proved troublesome however, so we discontinued it—replacing it with 30 mg. phenobarbital b.i.d. Two weeks later, he had no complaints, and the blood pressure readings were in the normal range (126/82 sitting and 132/84 recumbent). However, on the next visit, another month later, blood pressure was again in the hypertensive range. On questioning, he admitted that he had neglected to take his medication for the past three weeks because he thought he was "cured." His poor prognosis was again emphasized, especially in view of the family history, and he left, promising to continue on the medication. To date, he remains well controlled with mild sedation, but still needs continuous reminders about the need for treatment.

Comment

Such hypertension, in its early stages, is elusive and apparently benign. It produces no physical discomfort and may not even register on the sphygmomanometer, except sporadically. So, while it is quickly responsive to treatment with the mildest of sedatives, it presents a serious problem in that patients remain unconvinced of its importance and frequently progress to severe hypertension simply because of neglect. Perhaps the most important part of managing such patients is relentless follow-up.

3. Malignant Hypertension

A 59-year-old chauffeur was admitted to the hospital complaining of dyspnea, nocturia, fatigue, increasing blurring of vision, and headache which was present in the morning and grew progressively worse during the day. Blood pressures on admission were 240/124 recumbent and 232/128 standing; pulse was 120. He showed edema of both optic discs and retinal hemorrhage with sclerosis of the retinal arteries. The heart was enlarged to the left with EKG evidence of left axis deviation. Blood urea nitrogen was 27 mg.%, urine showed a trace of albumin, and the phenolphthalein excretion in two hours was normal.

We began treatment immediately with a ganglionic blocker, mecamylamine, 10 mg. b.i.d. After four days, blood pressure was slightly reduced but still over 200 systolic and 100 diastolic. His headaches were still present, so the dosage was increased to 12.5 mg. b.i.d. This produced further reduction to 205/102 recumbent and 160/84 standing (repeat BUN was 30 mg.%). However, he complained of marked constipation and some blurring of vision, and said he felt faint and lightheaded when standing. We decided at this point to give up ganglionic blockade and to attempt control of hypertension by chemical sympathectomy with guanethidine. At 2-day intervals, we reduced the dosage of mecamylamine by 5.0 mg. per day and gradually increased the dosage of guanethidine by 5 mg. After 10 days, the patient was taking 25 mg. doses of guanethidine alone, twice a day. He was fairly comfortable on this regimen except for a mild diarrhea. After three days of stable blood pressure, we increased dosage to two 25 mg. tablets as a single dose after breakfast. After another week, the blood pressure began to rise again, so two more 25 mg. tablets were added to the daily dose. At this dosage the blood pressure appeared to be stabilized at 186/98 recumbent and 158/82 standing. The diarrhea was controlled with the addition of

5 mg. homatropine. He was discharged from the hospital and followed in the clinic at biweekly intervals. His blood pressure remains reasonably stable, but dyspnea and headache still occur occasionally.

Comment

Hypertension of this severity responds only partially to any treatment and continues to progress. In spite of repeated adjustments of doses and drugs, the pressure will slowly rise. The best you can do is to get the blood pressure down as low as you can, and as soon as you can, with the least hazard and discomfort. It is important to remember, however, that elevated blood pressure is just one symptom of hypertensive disease, so be wary of the natural temptation to concentrate just on rapid reduction of blood pressure. If it is reduced too abruptly, the effects of diminished renal, cerebral, and coronary blood flow may be even more harmful than the initial blood pressure. This is especially important in severe cases like patient No. 3. Such patients frequently develop renal failure as a result of diminished renal blood flow, and must be watched carefully for a rise in BUN. An important factor in avoiding precipitous changes in blood pressure is to make sure that all dosage changes and all withdrawals or substitutions of drugs are made gradually. Also, because treatment of these patients always involves very potent drugs, it is helpful to remember that there may be an advantage in combining several drugs with different sites of action; they may potentiate each other and make possible smaller, and less toxic, doses of each drug.

Incidentally, an important precaution when prescribing a drug like guanethidine is to warn against the concomitant use of sympathomimetic drugs such as are commonly found in nose drops and asthma medication. Experimentally, the latter drugs' pressor effects are enhanced by guanethidine and related compounds; their concomitant use could cause the serious complications of an abrupt rise in blood pressure. One final point—about hypertensive crises, such as encephalopathy or acute cardiac insufficiency—I find that dramatic results can often be obtained with parenteral (I.V. or I.M.) reserpine (2.5 to 5.0 mg.) or hydralazine (20 to 40 mg.) every 4-6 hours.

In summary, then, the rule is: begin therapy with the mildest and safest drug which will produce the necessary lowering of blood pressure. Generally, I find it best to start treatment of the uncomplicated hypertensive with mild sedatives and tranquilizers such as reserpine and phenobarbital. In more severe cases, I add more potent (and more toxic) drugs in the following order: oral diuretics (thiazides); an arteriolar relaxant (hydralazine); chemical sympathectomy (guanethidine); and finally ganglionic blockers (chlorisondamine, pentolinium, mecamylamine) in selected cases.

CORRESPONDENCE

As a service to readers, CONSULTANT's authors will try to answer any question pertaining to their topics.

Write to: CONSULTANT
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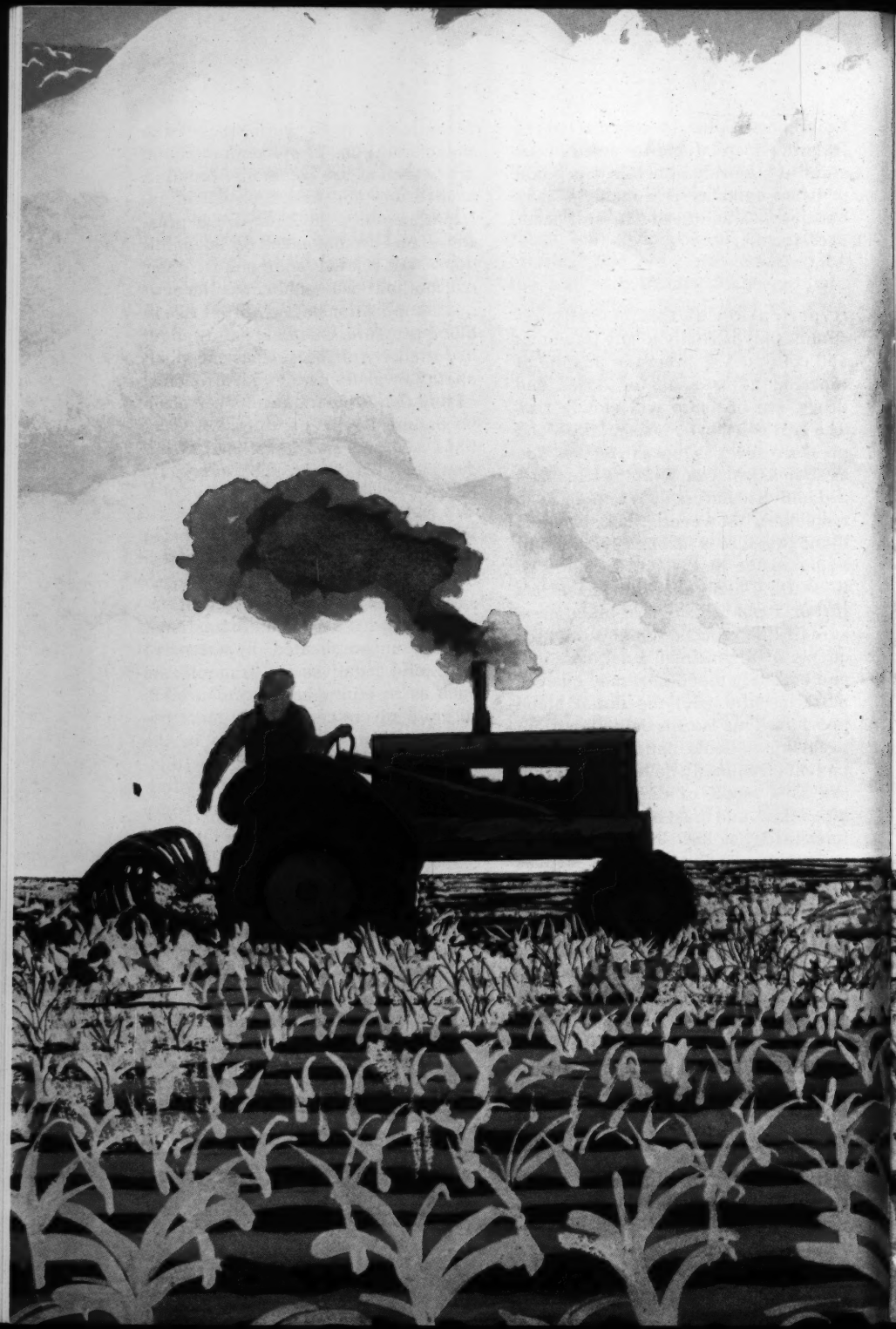

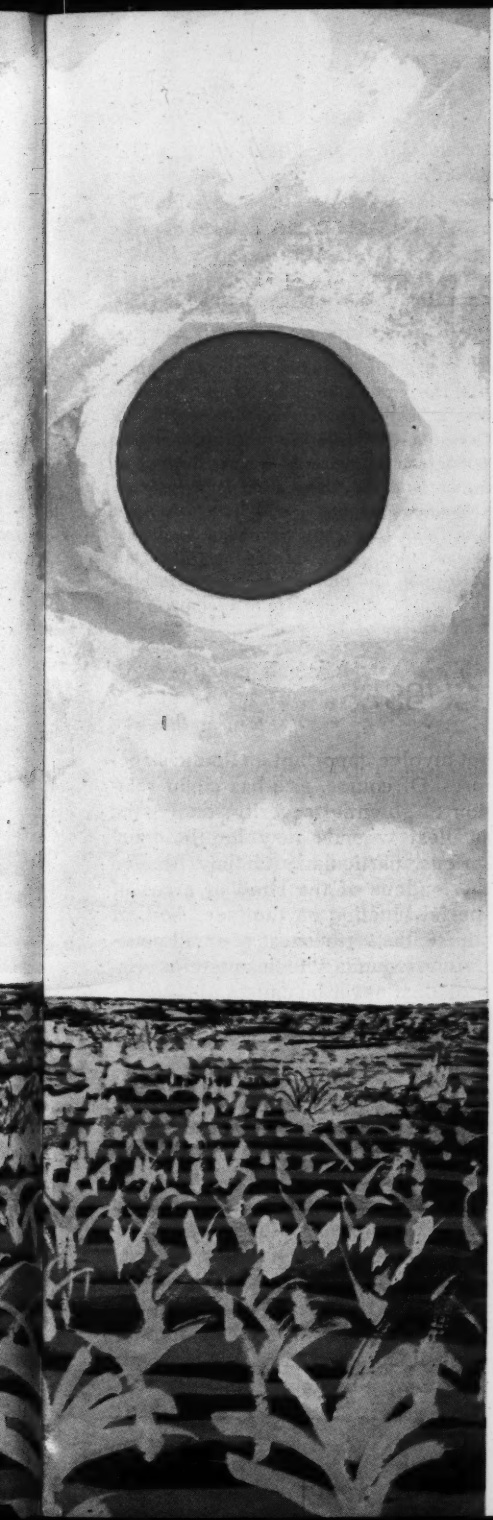

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Ayd, F.J., Jr.: Clin. Med. 6:387 (March) 1959.

For complete prescribing information, see back of magazine.

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SURGERY

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CUTS AND CUSSES

If you are like me, a bit frayed and frazzled, trying to maintain a regular schedule while engrossed in important and often unsolved medical problems, there is hardly anything more disconcerting than to be called on to handle a simple laceration. These cuts yield more than their share of cusses, and yet they must be managed. Since we are all faced with this problem, perhaps there are ways of reducing the irritations and at the same time improving our technique.

Management of simple wounds tends to deteriorate in several correctible areas: (1) *poor equipment,* (2) *poor timing,* (3) *poor follow-up,* and (4) *poor diagnosis.*

To begin in the reverse order: it is certainly disconcerting to discover that what appeared to be a minor wound is, in fact, major. By definition, a simple laceration is one that does not involve important anatomic structures. Of course, size has slight relation to potential severity; oddly, the smallest wounds may be the most serious, particularly if they involve the tendons of the hand or areas of special function on the face. And, of course, the seriousness of small penetrating wounds which enter the viscera must never be underestimated.

Sensible Follow-up Care

Without question, the follow-up care of a simple wound is at least as important as the techniques used in its initial repair. The first dressing should be changed within a few days because early inspection gives early clues of incipient or actual infection. The prophylactic use of antibiotics is never justified; antibiotics should be reserved for treatment of actual infection. Simple skin wounds seldom become infected even in the presence of heavy contamination.

The prophylactic use of tetanus antitoxin also can only be condemned. The purpose of tetanus antitoxin is to neutralize the toxin of the Clostridium organisms, and the toxin is never present at the time of the original injury. If tetanus invasion seems likely, the wound should be inspected at least every day. When and if evidence of tetanus infection appears, immediate hospitalization for wound drainage, administration of high potency broad-spectrum antibiotic therapy, and massive doses of tetanus *antitoxin* are clearly indicated. Of course, with any wound, a prophylactic immunization of tetanus *toxoid* should be given. This may act as a booster dose in the patient who has been previously actively immunized or, in an unimmunized person, will act as the first of a series of doses leading to active immunity.

Solving The Problem Of Emergencies

As far as I am concerned, a simple laceration is always poorly timed. What can be more upsetting than to have a patient rush into a crowded waiting room wrapped in a bloody towel, frantic and frightened? A simple solution to this problem is to have a back room to which the patient can be promptly removed. There you can assess the extent of the injury and, if the wound is simple, reassure the patient and allow him to rest and recover before repair of the wound is begun. If you are fortunate enough to have telephone notification of such a wound from someone qualified to determine its seriousness, a regular appointment at the close of the day's schedule can be arranged. If the wound is indeed simple, speed is seldom essential. A reasonable lag between the time of injury and repair will often result in a quiet and cooperative patient instead of an agitated and unhappy doctor-patient-wound relationship.

Nothing is more distressing – or unnecessary – than a painful procedure, which is usually the result of the patient's fear and the doctor's impatience. The wound should be carefully infiltrated with 1% procaine and 15 drops of injectable adrenalin to the ounce. Any wound must also be repaired with the patient in the recumbent rather than the sitting position. With adequate anesthesia in a field made bloodless by adrenalin, the wound can be excised and lightly undermined to produce an adequate sewing edge. The skin can then be approximated with closely placed interrupted sutures of 4-0 or 5-0 atraumatic nylon. If in the course of repair some blood vessels continue to bleed, they can be ligated by transfixion sutures of atraumatic plain 4-0 gut.

Do Away With Archaic Instruments

Chances are, equipment for repairing wounds in the office (and even in the emergency room of some community hospitals) has not been recently reviewed and replaced. If instruments are archaic, cuts and cusses are of equal frequency.

To repair any simple laceration, the following are essential:

1. a #15 Bard-Parker knife blade and #3 handle
2. the finest Adson dura forceps with teeth
3. Stevens tenotomy scissors
4. a fine diamond jaw needle holder
5. a simple skin hook
6. a 5 cc. Luer-Lok syringe
7. a new 24- or 26-gauge needle
8. 4-0 plain atraumatic surgical gut
9. 4-0 atraumatic nylon

10. 5-0 atraumatic nylon
11. 6 mosquito hemostats
12. 4 surgical towels
13. 12 3x3 sponges
14. 30 ml. medicine glass
15. 1 metal cup
16. 1 ampule of injectable adrenalin
17. gloves
18. aqueous Zephiran®
19. Mayo stand, tray, wrapping, linen, and sterilizing facilities

Just one last word: let us never forget that patients may be patient; often doctors are not. Cuts can be cleanly repaired and the cusses sharply reduced by the proper preparation of a simple laceration set, a quick inspection to determine the involvement of important anatomic structures, arrangement for a quiet and cooperative patient, and repeated follow-up of the wound itself.

QUESTIONS AND ANSWERS

Q. *When should sutures be removed?*

A. That depends on the appearance of the wound. Wound healing is never complete in less than fourteen days, and, if sutures are removed before this, steps should be taken to support the edges of the wound during the period of final healing. This is best done by the application of transverse gauze strips cemented by collodion (U.S.P., not flexible) until healing has been attained. It is frequently advisable to leave sutures in place during the entire 14-day period.

Q. *You suggest nylon sutures. Is there a place for other material?*

A. I select nylon as the primary skin suture because of its elasticity. Any wound swells to some degree. Newer fibers which are thixotropic (having "molecular memory" such as polyethylene) expand but then contract. Other suture materials, such as annealed stainless steel wire, silk, or cotton, are basically inelastic and will commonly produce stitch marks as a result of resistance against normal postoperative swelling.

Q. *Do you ever use sedatives before the repair of a simple laceration?*

A. Of course. A frightened patient can always be quieted. The judicious and careful use of morphine can only be recommended. The "hold-and-holler" techniques widely employed have no place in modern therapy.

Q. *Specifically, where can one buy the equipment you suggest?*

A. A more detailed list of the suggested set, and its source of supply, is available on request. Write to me in care of CONSULTANT, 1500 Spring Garden Street, Philadelphia 1, Pa.

Q. *You state that tetanus antitoxin is never acceptable. What about possible medicolegal action?*

A. There is abundant evidence in the medical literature that tetanus antitoxin is not only ineffective in the classic 1500-unit dose, but also potentially dangerous. Any litigation on this point can, as of today, be rather easily refuted.

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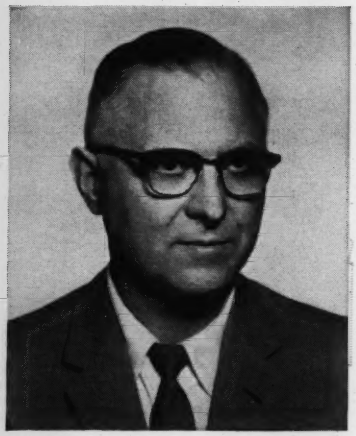
PSYCHIATRY



Robert L. Garrard, M.D.
Greensboro, North Carolina

Robert L. Garrard is a Fellow of the American Psychiatric Association, a member of the American Academy of Neurology, and is a past president of the Guilford County Medical Association. He received his medical training at Harvard Medical School. During World War II, he served as a Lt. Colonel (MC) with the U.S. Army in the European and Pacific Theatres of Operation. He is currently in private practice and has considerable interest in forensic medicine and psychiatry.

PSYCHIATRIC REFERRAL: A FEW IMPORTANT GUIDELINES

No doubt you are familiar with much of the advice that has been published in abundance concerning your approach to the treatment of patients with mental and emotional illnesses. There is certainly no shortage of articles that will tell you that you must be interested in the patient; that you must be willing to listen; that you should not attempt deep analytical probing but that you should provide supportive therapy while avoiding the temptation to do too much directive therapy; that you should never attempt any psychotherapy in patients you cannot tolerate or find irritating; that you must examine your own desires and decide whether you are really willing to do psychotherapy in the first place; and, of course, that you must not attempt to treat patients who have serious psychiatric problems that are beyond your competence. I suspect, though, that most (and probably all) general practitioners have a clear idea of their limitations in psychiatry and are only too happy to refer patients with serious problems to a psychiatrist.

But let's say you've made up your mind to refer a patient to a psychiatrist. Are there still some things you, and perhaps only you, can do to help the patient? I think so, and I hope these guidelines will prove practical.

Prepare The Patient

While education has greatly reduced the stigma attached to mental illness in the lay mind, there are still many

people who fear psychiatric care or to whom the need for such care connotes failure or weakness and seems shameful – hardly helpful attitudes. One of the first and most important things you can do, then, is help the patient and the psychiatrist get off on the right foot. Anything you can do to reduce a patient's fear or to motivate him to want to get well and accept treatment will be valuable. Exactly how you do this will vary from patient to patient, but just as your discussion of sex is easier and less shocking to a patient if you use scientific terms, so will your discussion of this problem be easier if you avoid emotionally charged words.

To some patients, you may have to explain that mental illness can take many forms, and brief the patient on what he can expect the psychiatrist to do. It may be helpful to remind your patient of how universal the problem of mental and emotional disorders is, and emphasize that his problem is not a sign of weakness. You might add a note of flattery (depending on the patient's status, of course) by mentioning that the incidence of such problems is higher among professional and executive people than among the non-skilled. Perhaps describing the improvement experienced by another patient who had a similar problem would help. It may be wise, if it is true, to reassure him that referral need not mean hospitalization.

However you choose to approach this problem, frankness is almost always better than deception. Attempts to conceal the fact that the psychiatrist *is* a psychiatrist, for example, are seldom successful, and when the patient sees through the deception he almost always reacts unfavorably.

Advise The Family

The patient's family usually needs advice, too, and you are in the best position to give it. Although the cooperation of a responsible relative may be absolutely necessary only when referring severely disturbed psychotic patients, you should always explain the situation to the family as completely as circumstances will permit and enlist their support.

I realize that you may run across a frankly hostile relative to whom you should not give information that may be used against the patient, but destructive influences in the home that may negate progress in treatment are usually caused by ignorance rather than malice. It is difficult, for example, for some relatives to accept that the patient is sick and in need of treatment rather than discipline. Often, it is a troublesome home environment that precipitated the patient's breakdown in the first place, and it is of little benefit to help the patient only to re-expose him to the cause of his illness. (Occasionally, indeed, a relative may need treatment as much as the patient.) By discussing the problem with the family you may uncover and perhaps eliminate trouble spots.

You may find it helpful to recommend one of several good books on mental and emotional illness that have been written for the layman. For example: EMOTIONAL ILLNESS: HOW FAMILIES CAN HELP by Beutner and Hale (Putnam – $2.50), MENTAL HEALTH IS A FAMILY AFFAIR, by Pratt and Neher (Public Affairs Pamphlet No. 155 – 25¢), WHEN YOU GROW OLDER, by Lawton and Stewart (Public Affairs Pamphlet No. 131 – 25¢). See footnote* on next page.

Provide A Good Case History

You should provide a thorough case history, including personal information that you might not, perhaps even *should* not, send to another specialist — a surgeon, for example. Mental illness serious enough to require treatment by a psychiatrist does not develop overnight. While some single event (divorce, being fired, death of a loved one) may make the illness flare up, the basic problem has been smoldering for some time, and anything you can tell the psychiatrist about the patient's background, childhood deficiencies, family and occupational difficulties, sex problems, resentments, etc., will be helpful. By telling the psychiatrist at once things that might otherwise remain concealed or be disclosed by the patient only after long and searching interviews, you may contribute substantially to the value of treatment and save the patient considerable time and expense.

Referring physicians seldom fail to tell me about the socially unacceptable incidents in a patient's background: he's always getting into fights; he drinks too much; he's been unfaithful. Less frequently, though, do they tell me that a patient is too good to be true: the adolescent who never gets into trouble; the man who is always reading the Bible and goes to church every day; the model husband who never argues about anything, either in the home or out. My point is not that any of these is a definite indication of psychiatric illness, but that the extreme in either direction — "good" or "bad"—*may* be significant.

QUESTIONS AND ANSWERS

Q. *What should I do when I refer a patient to a psychiatrist and the patient visits him once or twice and then rejects him?*

A. Try to find out why he has rejected him and, if you can overcome the patient's objections easily, do so. If you can't, though, don't try to force him to return, but suggest a different psychiatrist, perhaps one in some other community. Incidentally, if you send the patient to someone else, be sure to tell him that the patient has rejected another psychiatrist.

Q. *What should I do while the patient is seeing the psychiatrist?*

A. If the patient does not want to lose or interrupt his relationship with you, you should continue to see him. Ordinarily, though, you should limit yourself to reassuring the patient, and his family if necessary, and explaining the psychiatrist's reports to the family in terms they can understand. Whatever you do, avoid letting the patient put you in the position of contradicting the psychiatrist. If he tells you something about the psychiatrist's treatment that seems unreasonable to you, withhold judgment (or at least, comment) until you've checked with the psychiatrist. The patient's version, after all, may be distorted, or what seems unreasonable on the surface may be quite reasonable once it is explained.

*Single copies of the two Public Affairs Pamphlets mentioned in this article may be obtained free of charge from CONSULTANT, Smith Kline & French Laboratories, 1500 Spring Garden St., Philadelphia 1, Pennsylvania.

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'Acnomel' Cream is a basic topical preparation for acne treatment. Sulfur and resorcinol reduce oiliness, dry the skin and produce a keratolytic effect. Hexachlorophene reduces the possibility of bacterial infection.

Grease-free, easy to apply and to remove, flesh-tinted 'Acnomel' Cream conceals acne lesions as it heals them. Thus patient embarrassment about unsightly acne pimples and blemishes is greatly relieved.

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TWO CONVENIENT FORMS: 'Acnomel' Cream (sulfur, 8%; resorcinol, 2%; hexachlorophene, 0.25%; in a stable, grease-free, flesh-tinted vehicle). Standard strength for home application, morning or night. 'Acnomel' Cake (sulfur, 4%; resorcinol, 1%; hexachlorophene, 0.25%; in a washable, flesh-tinted cake base). Half-strength, in handy plastic containers, for convenient use away from home.

ADMINISTRATION: Cream: One application daily is usually sufficient. Patients with oily skin may apply more often. Apply in small amounts with finger tips. Keep out of eyes and off eyelids.

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To shorten the course of acne therapy, 'Acnomel' Cream may be prescribed for application at night and 'Acnomel' Cake for daytime use.

CAUTIONS AND CONTRAINDICATIONS: Moderate erythema and scaling are normal and are expected results of 'Acnomel' therapy. However, should these reactions become excessive, the patient should apply 'Acnomel' less frequently or discontinue until they subside. 'Acnomel' should not be applied to diffuse, acutely inflamed areas. Keep out of eyes and off eyelids.

AVAILABLE: Cream—in specially lined 1½ oz. tubes; Cake—in convenient 1 oz. plastic containers.

Prescribing information adopted January 1961.

GASTROENTEROLOGY

Sherman M. Mellinkoff, M.D.
U.C.L.A.

Since 1957 Sherman Mellinkoff has been Associate Professor of Medicine at the University of California at Los Angeles. He received his degree and residency training at Stanford Medical School, and was Instructor of Medicine at Johns Hopkins Hospital, where he also served as Chief of the Gastrointestinal Clinic. A member of the American Federation for Clinical Research, he has published 56 articles and is author of the book THE DIFFERENTIAL DIAGNOSIS OF ABDOMINAL PAIN (McGraw-Hill).

METABOLIC CAUSES OF SEVERE ABDOMINAL PAIN

Severe abdominal pain may reflect nothing more serious than pylorospasm after a hectic day with small children, or it may mean that to delay surgery for very long is to invite death. Of course, in many conditions the cause of the pain is evident from its location and the accompanying physical signs, but sometimes both the anatomical location of the pain and the physical signs are misleading. Especially confusing in this respect is the severe abdominal pain that may be produced by *metabolic disorders*. Some of these disorders and the type of pain they may cause are briefly reviewed here.

Electrolyte Imbalance

In some people almost any type of fluid-electrolyte abnormality will cause abdominal pain that is sufficiently severe to tempt the most conscientious surgeon. The immediate cause of the pain is probably spasm, paralysis, or dysrhythmia in the smooth muscle of the bowel or stomach. These elements may be mixed in various proportions; they may be localized to one part of the G.I. tract or generalized. About the only general statement that can be made, therefore, is *that the physician must consider electrolyte imbalance whenever abdominal pain appears in a situation likely to upset the homeostasis of water and minerals.* The following example is the essence of an actual case: A 19-year-old girl had nausea, vomiting, and diarrhea during an epidemic of "intestinal flu". As the vomiting subsided, she drank large amounts of water but was afraid that

juices would aggravate her diarrhea and that milk, soup, or solid food would provoke the vomiting again. Her abdomen was grossly distended with tympanites, and she complained of generalized abdominal pain, nausea, and weakness. When the serum potassium was found to be very low, intravenous fluid and potassium were administered. Electrolyte repletion relieved her pain, deflated the bowel, and restored her appetite.

Uremia

Disorders of electrolyte, fluid, or acid-base balance are often induced by uremia, and can cause many kinds of abdominal pain that vary widely in location, intensity, and frequency. Correction of the electrolyte imbalance may afford relief, but not always; intermittent pain may persist in spite of therapy. Surgery, sometimes considered as a last resort under these circumstances, will do no more than add to the patient's discomfort. In the long run, the causes of abdominal pain in uremia frequently remain a mystery, and the pain itself can only be treated symptomatically.

Hepatic Failure

It is well known that liver disease can cause right upper quadrant pain or epigastric pain due to distention of the liver capsule. What is not so well known is that hepatic failure can sometimes—in other ways by no means clear—cause severe abdominal pain. These attacks, which may imitate intestinal obstruction, are seen in fulminant or rapidly progressive hepatitis, Laennec's cirrhosis (usually with ascites), and in hemachromatosis. Idiopathic jaundice, the so-called "Dubin-Johnson syndrome," which is characterized by chronic jaundice and a brown pigment in the liver, will also often cause intermittent pain in the right upper quadrant.

Hemachromatosis

The abdominal pain caused by hemachromatosis is usually mild but at times can be severe. The severe pain may be caused by bouts of pancreatitis or by cancer of the liver, two complications of the conditions, but often no such reason for the abdominal pain is found. Because cirrhosis always accompanies hemachromatosis and diabetes mellitus frequently does, this diagnosis should always be considered whenever both are present. Sometimes the cirrhosis may be so inconspicuous that it escapes detection, but ordinarily the BSP test will suggest liver disease. Hemachromatosis is also manifested by a high serum iron and a very high saturation of the serum iron-binding capacity. Usually, the clinical picture and the tests mentioned above will establish the diagnosis; but, if not, liver biopsy with special iron stains can be utilized.

Diabetic Acidosis

Electrolyte imbalance, dehydration, and ketosis are known to cause abdominal pain in diabetic acidosis, but there are probably other factors as well. In addition, diabetic acidosis may itself be precipitated by a genuine intra-abdominal disease, such as appendicitis. Emptying the stomach and treating the diabetes vigorously usually relieves the abdominal pain swiftly, or prepares the patient for surgery if signs of peritoneal irritation are really present.

Addison's Disease

Adrenocortical insufficiency frequently announces itself with vague,

neurotic-like gastrointestinal symptoms of various types. Sometimes it causes attacks of severe abdominal pain, which simulate an acute abdomen, although convincing signs of peritoneal irritation are generally absent. Usually one can find hyperpigmentation, often in patches on the buccal mucosa, which, together with hyperkalemia, should arouse one's suspicion and lead to more specific tests.

Porphyria

The attacks of severe abdominal pain caused by acute intermittent porphyria may either be steady or cramping. The pain may radiate to the chest, back, or thighs. Marked constipation is the rule; vomiting is common. Paroxysmal hypertension, slight fever, leukocytosis, and faint jaundice may appear. Sure signs of peritoneal irritation are absent, but peristalsis may cease. A urine sample obtained during the attack may be red or may turn black on standing in the sunlight. But because the urine may be normal-colored, the Watson-Schwartz test, which is simple and inexpensive, is considered a more reliable screening test. However, it is not always infallible, and if there is any doubt in the interpretation of the test, or if the clinical picture is not perfectly clear, more definitive study of the patient's porphyrins should be done.

Idiopathic Hyperlipemia

Also generally considered to be caused by an inborn metabolic error, idiopathic hyperlipemia can cause attacks of severe abdominal pain, sometimes with fever and leukocytosis. Acute pancreatitis, with an elevated serum amylase, may or may not be present. Pancreatitis of any cause may also cause hyperlipemia. So, although the patient who has acute pancreatitis may have milky blood serum in the hematocrit tube, one must find out if lipemia persists in pain-free intervals in order to establish the diagnosis of idiopathic hyperlipemia. As a rule, the total serum lipids are elevated out of proportion to the blood cholesterol concentration, which may be high or normal. Hepatosplenomegaly, cutaneous fat deposits, and a family history of the disorder are diagnostic aids, but these findings may be absent in an otherwise typical case.

Familial Mediterranean Fever

Familial Mediterranean fever is another error of metabolism known by many names, including periodic peritonitis, periodic disease, and familial polyserositis. (It is not to be confused with lupus erythematosus.) Attacks of abdominal pain due to a sterile peritonitis with fever and sometimes leukocytosis usually begin in childhood. Attacks ordinarily last 12 to 24 hours, but occasionally as long as 3 or 4 days. Between attacks the patient is perfectly well, but the attacks may vary in frequency from several a week to sporadic or rare. The illness is almost always found in persons of Mediterranean ancestry, most often Armenians, or Jews who trace their ancestry to Spain or Iraq. Besides the attacks of peritonitis, similar febrile paroxysms may occur with pleuritis (causing severe chest pain), arthritis that disappears without sequelae, or a temporary erysipelas-like dermatitis of the legs or feet. The disease is a little more common in men than in women. It usually vanishes during pregnancy, but does not respond to adrenal steroid therapy. A rigid and very low fat diet usually causes great improvement, for reasons that are by no means clear.

QUESTIONS AND ANSWERS

Q. *Which of these metabolic disorders are most likely to be seen in children?*

A. Electrolyte disorders would be the most common. Familial Mediterranean fever, although not a common disease, does occur fairly frequently in certain susceptible populations and in the United States is seen mostly among those of Armenian descent. About 70% of these patients are 10 years of age or younger when the abdominal pain first occurs.

Q. *Is there any theory to account for absence of abdominal pain during pregnancy in women who have familial Mediterranean fever?*

A. The disease presents a puzzling research problem. There are many theories but few facts. Unfortunately, pregnancy is an impractical and rather impermanent form of therapy.

Q. *Are there many other metabolic* disorders that can cause abdominal pain?

A. Yes. Some of these, like cystinuria, do so by causing specific gross lesions—in this case kidney stones which are radiolucent and, therefore, often overlooked. Gout is another such disease and the uric acid stones are also radiolucent. In familial pancreatitis (probably an inborn error of metabolism) the pancreas is grossly abnormal during acute attacks of pain and ultimately may become permanently abnormal. In other metabolic diseases, such as mastocytosis or urticaria pigmentosa, the cause of the abdominal pain is neither grossly visible nor even known.

Next month in CONSULTANT:

Picking the Schizophrenic Before He Is Psychotic—by Ainslie Meares, M.D., Melbourne, Australia, tells how to recognize early and often overlooked signs of this terrible illness:

"Schizophrenic thinking is often very literal . . . If we ask the patient the meaning of, 'When the cat is away the mice will play,' he is likely to talk about cats and mice."

When starting thyroid replacement therapy in hypometabolism or hypothyroidism . . .

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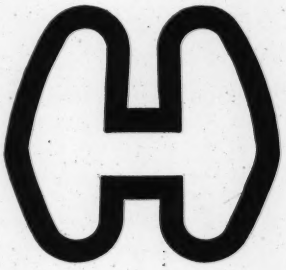

PRESCRIBING INFORMATION

ADMINISTRATION AND DOSAGE: Dosage should be adjusted according to the severity of the condition and the response of the patient.

Most patients should be started on 25 mcg. of 'Cytomel' daily. To increase dosage to recommended maintenance levels for these patients, increments of 12.5 or 25 mcg. may be made in the daily dosage at intervals of one or two weeks. Dosages in the range of 100 mcg. daily, and higher, are well tolerated by many patients.

When starting dosage is 5 mcg. daily (as in myxedema, male infertility, simple goiter and in patients being switched from thyroid, L-thyroxine, or thyroglobulin), increments of 5 or 10 mcg. may be made in the daily dosage at intervals of one or two weeks. When dosage reaches 25 mcg. daily, increase as described above.

'Cytomel' is usually administered in divided doses.

Note: In geriatric patients or in children always start with 5 mcg. daily and adjust dosage in increments no greater than 5 mcg.

Indication	Recommended Starting Dose	Recommended Maintenance Dose
Hypometabolism Mild Hypothyroidism	25 mcg. daily	25-75 mcg. daily (Smaller doses may be fully effective in some patients.)
Myxedema	5 mcg. daily	50-100 mcg. daily
Female Reproductive Disorders	25 mcg. daily	25-50 mcg. daily
Male Infertility (Based on sperm count or sperm motility responses after two to four weeks of treatment at a given dosage level, the daily dosage may be increased by 5 or 10 mcg. If after further treatment the desired response has still not been obtained, the daily dosage may again be increased. Although total daily dosage usually need not exceed 25 mcg., as much as 50 mcg. daily may be used if necessary.)	5 mcg. daily	10-25 mcg. daily
Simple (non-toxic) Goiter	5 mcg. daily	25-75 mcg. daily

SPECIAL CONSIDERATIONS AND CAUTIONS: Tachycardia, excitability, headache, or excessive sweating are signs of overdosage. Medication should be interrupted until the unpleasant symptoms disappear, and then resumed in smaller doses. Since the return to pretreatment status is rapid, 'Cytomel' can usually be resumed at the desired dosage after one to two days.

When a subnormal BMR exists as part of the clinical syndrome of hypometabolism or hypothyroidism, administration in excessive dosage will cause elevation of BMR to levels above normal.

'Cytomel', unlike various forms and fractions of thyroid, will not cause elevation of the blood protein iodine level.

Endogenous thyroid gland function, reflected particularly by I^{131} uptake, may be depressed by 'Cytomel' administration. Depression of this function is most apt to occur with higher dosages (greater than 75 mcg. daily). Experience to date indicates that this effect is not clinically harmful. There have been no unfavorable sequelae in reported instances where 'Cytomel' therapy has been discontinued after depression of I^{131} uptake occurred. In such cases this function has promptly returned to normal after discontinuance of 'Cytomel'.

Since 'Cytomel' is physiologically related to thyroxine, it is not recommended for use in the presence of angina pectoris, in other cardiovascular disorders, or ischemic states. However, if it is used in the presence of such conditions, the starting dosage should never be more than 5 mcg. daily. If dosage is increased, it should be in increments of no more than 5 mcg. daily at approximately two-week intervals.

Hypopituitarism, morphologic hypogonadism and nephrosis should be ruled out before 'Cytomel' is administered.

CONTRAINDICATION: Addison's disease.

FORMULA: Each 'Cytomel' tablet contains 5 mcg. or 25 mcg. of liothyronine (L-triiodothyronine or LT3), as the sodium salt; 25 mcg. of 'Cytomel' is calorigenically equivalent to approximately 1 gr. of thyroid.

AVAILABLE IN TWO DOSAGE STRENGTHS: 25 mcg. (scored) tablets in bottles of 100 and 1000; 5 mcg. tablets in bottles of 100.

Prescribing information adopted Jan. 1961

SK&F Smith Kline & French Laboratories

from the menarche to the menopause

From the beginning of the menstrual function until its cessation, iron deficiency is more common than is often suspected. Among the prime causes in young women are, of course, menstruation, pregnancy and lactation.

Iron and iron alone is all that's needed to correct iron-deficiency anemia. The superior form of iron is 'Feosol' in 'Spansule' capsules.

For example, in a series of pregnant patients treated with 'Feosol' *Spansule* capsules 83% had good to excellent hematinic response. Due to virtual absence of side effects and convenient once-a-day dosage, patient acceptance was high. Smith Kline & French Laboratories.

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brand of ferrous sulfate — brand of sustained release capsules

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ORTHOPEDICS

Harvey P. Kopell, M.D.
New York University

Harvey P. Kopell is Associate Professor of Orthopedic Surgery at New York University School of Medicine, and is active in the Neuro-Muscular Study Group at the New York University Bellevue Medical Center. He is associate visiting orthopedic surgeon, Bellevue Hospital, and assistant attending orthopedic surgeon, University Hospital. Dr. Kopell is a member of the American Academy of Orthopedic Surgeons and the American College of Surgeons. One of his special fields of interest is the diagnosis of peripheral-nerve-entrapment phenomena.

THE LOW-BACK COMPLEX— UNDERSTANDING IT BETTER

The "low-back complex" is a lumbar spine derangement that accounts for the majority of common back complaints. It may respond to conservative measures, or it may require special treatment. Telling in advance which is which may be extremely difficult because the mechanisms involved are complex and the sources of pain — the key to differential diagnosis — are elusive. When pain is local, common measures to reduce inflammation and relax muscle spasm usually provide relief. But when it is radiating as well, proper treatment depends on determining the pattern of pain, and to do this requires an understanding of the pathology.

Joint Parts At Fault

The low-back complex is a joint derangement brought about by a malfunction of the spinal muscle-ligament system; in short, two sets of muscles that are supposed to work together smoothly somehow fail.

A derangement of the lumbar spine is a joint derangement. There are three parts to a true joint: First, the bearing surfaces and their enclosure — the synovia and capsule. Second, the fulcrum-establishment or stabilizing mechanism of the joint that maintains proper relationship of the bearing surfaces to each other. Third, the motor power that moves the joint, or maintains the gross position of the two arms of the joint.

To appreciate the importance of a stable fulcrum, one has only to shut a heavy two-hinged door when one of the hinge pins is missing or a hinge plate is loose. Even though the bearing surfaces are intact and the motor power is adequate, the door will not

close smoothly. To make up for the unstable fulcrum requires a substantial, awkwardly directed motor power or force. Such a force may jam the door; jamming, in the case of joint motion, may mean a muscle spasm.

Joint Action Of Spinal Muscles

Basically, two sets of muscles and associated ligaments control spinal movements. One, which binds only adjacent vertebrae together, acts to stabilize the fulcrum. The other – a larger group of muscles – crosses and joins several vertebrae to make up an articulated spinal segment and provide motor power to move it, or to maintain the position of the spinal column in relation to the pelvis and upper trunk.

The trouble comes when the set of motor muscles acts before the stabilizing group of muscles can provide a stable fulcrum. Jamming results. To make matters worse, the motor muscle unit then tries to take over to stabilize the fulcrum, but does not provide a proper force vector to maintain the bearing surfaces together. Abnormal joint motion results, which in turn may affect an intervertebral disc.

The disc, which acts like a shock absorber, serves to smooth out or limit the rate of joint movement. Fibers in its ring are in two groups which spiral in opposite directions and so cross each other along a vertical axis, somewhat like an Oriental finger trap. As in the finger trap, the fibers remain intact to a tensile, compressive, or torsional force, but tend to be deformed and weakened by shearing forces, which may result from faulty stabilization with inadequate muscular attempts at compensation.

Derangement of the overstressed or injured myoligamentous unit produces a local sterile inflammatory reaction which can cause pain. Abnormal motion adds to the distress.

Muscles that try to make up for the unstable fulcrum are another source of local pain. They work hard, but their direction of force is not exactly right to bring about stabilization, so spasm results. Spasm causes pain by exerting an abnormally strong pull against muscle attachments, or by producing a relative ischemia, because the spinal muscles do not have the intrinsic vascular status to maintain good circulation for continued contraction. Spasm may aggravate local pain by exerting an improper force against the joints.

Localized Pain

Use of an anti-inflammatory agent, such as hydrocortisone, systemically or locally by infiltration, can allay inflammation in the deranged fulcrum-establishment mechanism.

Some mechanical disruption may persist because of compensatory muscle spasm, which in itself is painful and maintains the derangement. Spasm often perpetuates itself because the functional ischemia it produces increases both muscular irritability and stretch reflex. Spasm pain can be decreased by novocaine infiltration or measures to stimulate circulation (heat, counterirritants, ethyl chloride spray). It can be attacked directly by muscle relaxants or by manipulative procedures that overload and temporarily inactivate the stretch reflex mechanism. Reducing the spasm, if it has aggravated the derangement, will ease the extra stress on the myoligamentous stabilization system, allowing it to recompensate normally.

Radiating Pain

There are three basic causes of radiating pain associated with the low-back complex.

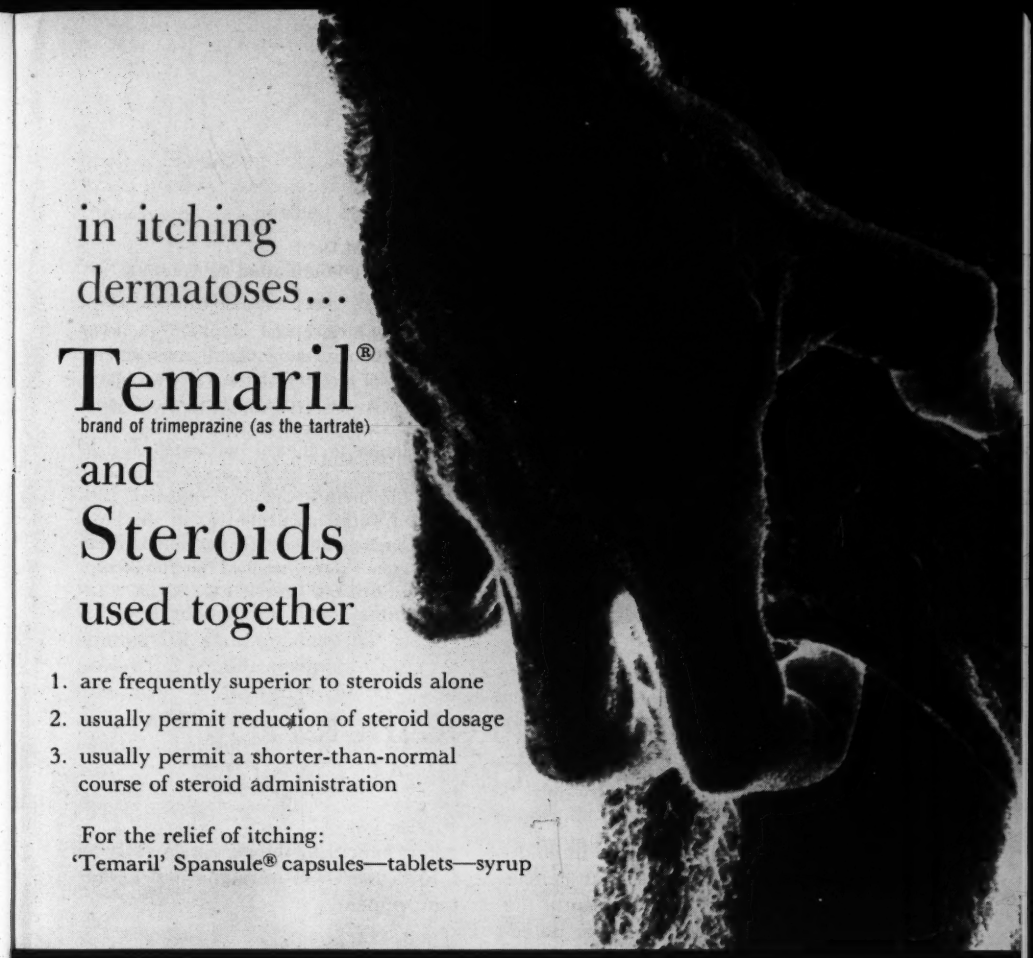
Pain associated with *irritated paraspinal structures* occurs at the attachment points of the spinal muscles and ligaments. Because of facilitation of pathway, the pain can be referred to a peripheral portion of the spinal segment. Therefore, a local spinal irritation can even cause sciatica. Pain of this sort should present no sensory deficit, motor atrophy, or reflex changes and can be relieved by infiltration of the paraspinal structures with a local anesthetic or an anti-inflammatory agent. The procedure here is both diagnostic and therapeutic. More than one injection may be needed and adjunctive treatment such as heat, muscle relaxants, and salicylates are useful. If such measures fail, then stabilization must be provided externally through a brace or internally by fusion.

In persons with a *herniated intervertebral disc,* pain and disability are usually referred to the terminal distribution of the affected nerve root. The resultant pain is soon accompanied by a radicular sensory deficit, motor weakness, and atrophy. When radiculopathy is not progressive, the patient often can be made comfortable by the usual adjunctive therapy, but when it is progressive, then laminectomy is necessary.

If local stabilization proves inadequate for the functional demands placed on the back after laminectomy, then fusion may be necessary.

Pain may be produced by *peripheral entrapment neuropathies* that develop in nerves that have an intimate relationship with muscles stabilizing the spine to the pelvis, or the pelvis to the femur. Those most commonly involved are the sciatic, iliohypogastric, ilioinguinal, and lateral femoral cutaneous nerves. Entrapment of nerves that have no muscular innervation will not produce atrophy. Sensory dysfunction occurs either as hypoesthesia or hyperesthesia, depending on the severity of the neuropathy and its duration. Sciatic neuropathy may be accompanied by peripheral motor changes that closely resemble those produced by the radiculopathy of a herniated disc, but with it, the gluteal musculature is spared. Blockage of the suspected nerve markedly reduces pain. Even so, differentiating neuropathy and a disc herniation between L4-5 and L5-S1 is difficult. If blockage brings only transient relief, then neurolysis is probably indicated to relieve the neuropathy. Since neuropathy often causes and reinforces postural abnormality, its removal by neurolysis may relieve the postural stress as well, permitting recompensation of the stabilization system and relieving local as well as radiating pain.

Once recovery has occurred, be it from a simple or complicated derangement, patients should be told to be careful about sudden and unusual lumbosacral stresses. Most, however, will be so anxious to avoid a recurrence, and understandably so, that they will tend to pamper their "weak backs." But because pampering interferes with reconditioning, you should encourage them to resume normal activity gradually, and to engage in such general exercises as walking and swimming, which, in turn, will promote muscular synergy and help ward off subsequent derangements.



in itching dermatoses...

Temaril®

brand of trimeprazine (as the tartrate)

and Steroids used together

1. are frequently superior to steroids alone
2. usually permit reduction of steroid dosage
3. usually permit a shorter-than-normal course of steroid administration

For the relief of itching:
'Temaril' Spansule® capsules—tablets—syrup

'Temaril' is an oral medication specifically for the relief of itching. It has been found effective in relieving pruritus accompanying dermatoses of allergic, inflammatory, metabolic, hemovascular and psychic origins, as well as those whose etiology is not clearly understood.

INDICATION: 'Temaril' is indicated for the treatment of mild and severe pruritus, whether acute or chronic.

DOSAGE AND ADMINISTRATION: Dosage with 'Temaril' should always be adjusted according to the severity of the symptom and the response of the patient.

	Usual Dosage	Resistant Cases
Adults	tabs.: 1 (2.5 mg.) q.i.d. caps.: 1 (5 mg.) q12h	tabs.: 2-4 q.i.d. caps.: 2-3 q12h
Children (ages 7-12)	tabs.: 1 t.i.d. caps.: 1 at night	tabs.: 2 t.i.d. caps.: 1 q12h
Children (ages 3-6)	tabs.: 1 t.i.d. syr.: 1 tsp. (2.5 mg.) t.i.d.	tabs.: 1 q.i.d. syr.: 1 tsp. q.i.d.
Children (ages 2 and under)	syr.: ½ tsp. t.i.d.	syr.: ½ tsp. q.i.d.

NOTE: Total daily dosage should not exceed 5 mg. for children ages 2 and under, 10 mg. for children ages 3-6, or 15 mg. for children ages 7-12. The physician should caution parents not to administer more than prescribed dosage to children.

When itching is a nighttime problem, larger doses (in adults: 5 or 10 mg.) should be administered at bedtime, with daytime dosage adjusted accordingly.

SIDE EFFECTS: Mild and temporary drowsiness may be encountered. Dizziness, dryness of the mucous membranes and gastrointestinal upsets have occurred occasionally. All of these effects usually disappear after a few days of medication. Persistent drowsiness may be overcome by reduction of dosage.

CAUTIONS: Clinical experience has demonstrated that 'Temaril', a phenothiazine derivative, has a wide margin of safety and that there is little likelihood of blood or liver toxicity, or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence, and patients should be kept under regular observation.

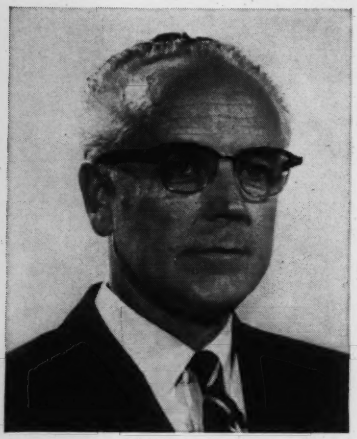
FORMULA: Each tablet and each 5 cc. teaspoonful of 'Temaril' Syrup contains trimeprazine, 2.5 mg., as the tartrate. (The syrup contains alcohol, 5.7%.) Each Spansule® sustained release capsule contains trimeprazine, 5 mg., as the tartrate.

SUPPLIED: Tablets, in bottles of 50 and 500; syrup, in 4 fl. oz. bottles; Spansule® capsules, 5 mg., in bottles of 30.

SK&F Smith Kline & French Laboratories

Prescribing information adopted Jan. 1961

SPECIAL FEATURE



J. Ernest Ayre, M.D.
Cancer Cytology Foundation of America

J. Ernest Ayre is medical and scientific director of the Cancer Cytology Foundation of America and also educational director of the Florida College of Medical Arts and Sciences. Since graduating from the University of Alberta, he has devoted special attention to clinical and cytobiological studies of cervical cancer. He served as director of McGill University's Cytology Research Laboratory and, later, as president of the Pan-American Cytology Society. He has authored 110 medical papers, three medical motion-picture films, and a textbook, CANCER CYTOLOGY OF THE UTERUS.

A 2-MINUTE PROCEDURE FOR DETECTING CERVICAL CANCER

One of the current tragedies in medicine, in my opinion, is that cancer continues to reap its toll despite the availability of new and better detection methods. One example is cervical cancer, which last year killed 17,000 women in the United States. If detected early—and it can be, by cervical cytology—this form of cancer is highly curable; the 5-year cure rate could be above 95%.

In this paper, I would like to describe, for readers not familiar with it, an office procedure for early detection of cervical cancer. The procedure is simple and painless. It requires only 2 minutes for collection of two cervical smears, plus a little time for fixing and mailing the specimens to a laboratory. The procedure is so reliable that it can detect cancer of the cervix as early as 5 to 9 years before signs and symptoms appear.

But before I describe the procedure and give some pointers about it, let me first draw a distinction between biopsy and cervical cytology. Biopsy is useful when signs and symptoms such as persistent bleeding and pain suggest cancer. Cervical cytology, on the other hand, is most useful as a screening test—not only for evaluating suspicious lesions and determining the need for biopsy, but also for detecting precancerous changes. An example of its effectiveness: a study in Memphis, Tennessee, used cervical cytology testing in 108,000 women, and 393 intraepithelial carcinomas were detected—90% of them totally unsus-

pected. In addition, cytology detected 373 invasive cancers, and 30% of these were unsuspected.

How To Collect The Specimens

First visualize the cervix, using a bivalve speculum. The speculum need not be completely dry, but care must be taken not to contaminate the cervix with lubricating jelly. Lubricating jelly may be placed on the lower outside blade, or else it may be applied to the introitus of the vagina, with the finger, as it is dilated before the speculum is inserted.

For collecting cellular specimens, either a pipette for aspiration or a spatula for scraping may be used. I prefer the spatula technique for routine tests. Notice that the key end of the spatula should be placed in the cervical opening and then rotated 360°

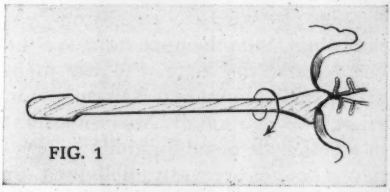


FIG. 1

so that it scrapes the entire squamocolumnar junctional circle. The first scraping will remove quite a bit of mucus. Contrary to some opinions, this sample should not be discarded, but rather preserved as the first slide; sometimes cells from the endometrium will be caught in the mucus plug and give positive or suspicious evidence of adenocarcinoma. A second scraping should then be done, using gentle pressure. This removes clusters of cells directly from the tissues of the squamocolumnar junction. In the presence of a large erosion where the wing of the spatula cannot reach the squamous epithelium, the squamocolumnar junction should be scraped with the opposite end of the spatula, under direct vision. With this procedure, myriads of cells are collected which, by cytological examination, may reveal even the smallest early cancer *in situ*.

Alternative methods include use of the cervical swab or the pipette. In my experience, the swab technique is not satisfactory, because it carries a risk of missing carcinoma *in situ*. Quite frequently, the swab will have absorbed its full quota of mucus and cells directly from the cervical mouth and will not attract additional mucus or cells from the edge of a moderate-size erosion. As a result, cells from the vital cancer predilection site may be missed. Also, swab smears are very thin and tend to provide too few cells for examination.

If a pipette is used, mucus should be aspirated from either the cervical os or from the vaginal pool where the volume of cytologic material is diluted in a greater volume of fluid and mucus. Many authorities advise against using a smear from the vaginal pool as the sole detection technique because it may miss 30% to 40% of preinvasive cancer of the cervix. This is particularly true if the patient has taken a douche before the examination. When a pipette is used, it should be clean and should have a small tapered opening. A pipette with a large opening is relatively unsatisfactory because the mucus sticks to the inside of the pipette and cannot readily be expressed despite repeated forceful pressure on the rubber bulb.

Causes Of Bleeding After The Procedure

I would like to stress that bleeding after the procedure is not a sign of

malignancy. Bleeding is most common with an inflammatory papillary erosion; the infected tissue is just as friable as malignant tissue and tends to bleed readily.

Bleeding sometimes occurs when a cut tongue-depressor is used instead of a cervical spatula for taking scrapings. Recently, I received two cytology slides on one patient successively from two different doctors. The first was almost entirely a blood smear and showed no suspicious or cancerous cells. The second was positive for cancer. Because of this unusual situation, I talked with both doctors and found that the first had used a cut tongue-depressor for cervical scraping and had encountered bleeding. The patient was so alarmed that she went to another physician, who took a smear with a cervical spatula in the conventional manner. The cancer was entirely missed by the first test, because active bleeding washed away the cancerous cells; whereas the other test proved positive for preclinical cancer. (The patient was promptly treated and cured.) This example illustrates the point that, if a tongue-depressor is used for scraping, the sharp edges should first be sandpapered.

Finally, bleeding can result from too vigorous scraping with a spatula. Gentle pressure is all that is needed to remove a rich sample of cells from the cervical mouth.

Fixation And Mailing

The two samples of cells and mucus should be transferred to glass slides and fixed by the conventional method of a 50-50 mixture of 95% alcohol and ether. The slides should be left in this fixative for at least 30 minutes, but they may be left for 12-24 hours or longer without harm. The slides should then be prepared for mailing to a local laboratory for staining and experienced cytodiagnosis. The mailing technique consists of using a drop of glycerine to seal off the entire smear area on the slide. A second clean glass slide should then be placed over the first, then the two should be wrapped together and sent in a cardboard container together with a history of the patient.

Incidentally, a short-cut method in fixing slides is the dry-fix method, whereby a commercial preparation (or 95% acetone) is applied directly to the wet smear and then allowed to dry in air. Two such preparations are Diaphane (Wills Corp.) and Cyto-dri-fix (Paragon).

The history accompanying the specimens should be as complete as practicable. The woman's age is the most important, then the appearance of the cervix, and the history of her menstrual cycle (whether it is normal or in what way abnormal). Also important is whether or not the patient is pregnant, or has recently delivered or aborted.

Positive Cytology Must Be Confirmed By Biopsy

If the cytology report is positive for cancer, no time should be lost in performing a biopsy on the patient. When there is a visible lesion, a punch biopsy may be used, but when there is no visible lesion and yet the cytology is positive, then a "ring-biopsy" should be used to obtain adequate material for confirmation. (See Figures 2 to 6 on opposite page.)

In conclusion, I would like to stress

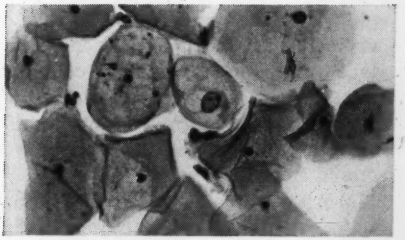


Figure 2 – Cervical-spatula smear showing *normal* cells from a healthy cervix. Note the uniform appearance of the small pyknotic nucleus in all cells. These cells are chiefly of the mature superficial cornified type. (Papanicolaou stain. x550)

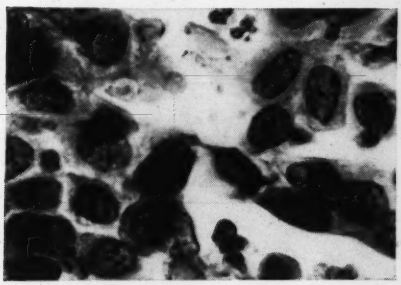


Figure 3 – Cervical-spatula smear from benign-appearing cervix which harbored preclinical early infiltrating epidermoid cancerous lesion (see Figure 5). Note the sharp contrast in appearance of the nuclei as compared to the normal cells in Figure 2. The nuclei are greatly enlarged, irregular in size and shape, and show a moderate degree of hyperchromatism. The cells exhibit intact cytoplasmic envelopes frequently observed in the pre-necrotic, pre-ulcerating stage. Cytologic diagnosis: conclusive evidence of malignancy. (Papanicolaou stain. x550)

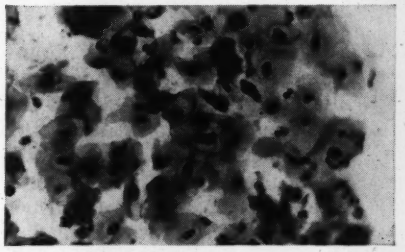


Figure 4 – Cervical-spatula smear showing cells whose appearance suggests extremely early anaplastic change described as "precancer cell complex" or "dyskaryosis". Note the moderate nuclear enlargement, irregularity and hyperchromatism in cells derived from the surface epithelium. This stage of precancerous activity merges with early carcinoma *in situ*. The cytobiology of premalignancy provides an ideal research approach to the discovery of "cause."

Figure 5 – *Preclinical Cancer of Cervix.* There is no "target lesion" for biopsy and cancer is already "early infiltrating". The spatula smear revealed the cells shown in Figure 3. There was no bleeding following the use of the cervical spatula.

Figure 6 – *Inflamed Papillary Erosion of Cervix.* The cells are entirely benign in the smear. This benign-type lesion frequently bleeds when the smear is taken. The cervix appears more suspicious than the cancerous lesion in Figure 5.

the following points about cervical cytology:

(1) The test should be given to every woman over 20 on her first visit to the office.

(2) It should be given routinely to pregnant women (regardless of the trimester they are in). It should also be given after pregnancy when the patient has her 6-month check-up.

(3) The patient should be told that the test does not mean she has cancer, but rather that it is a routine procedure for early detection and prevention.

(4) The technique of choice is the cervical spatula smear because it gives a rich concentration of cells for examination and a negative test is reliable. Cut tongue-depressors should not be used unless the sharp edges are sanded smooth.

(5) All positive diagnoses should be confirmed by biopsy, but biopsy in the presence of preclinical lesion must be adequate and must achieve total biopsy of the tissue material embracing the squamocolumnar junctional circle (ring-biopsy).

QUESTIONS AND ANSWERS

Q. *How reliable is cytology in detecting cancer?*

A. If the spatula technique is used, the percentage of false-negative diagnoses is extremely low, less than 1%. The test is not so reliable when only vaginal smears are used or when specimens are taken with a cotton swab. Almost all cervical cancer arises at the junction of the squamous and the endocervical epithelium, and for this reason, any technique used for collecting cellular specimens should concentrate on this area. With careful and regular collection of cellular specimens, cytology can virtually eliminate death from cervical cancer among your patients.

Q. *Isn't it impractical to expect a physician not near a large hospital to practice cytology screening?*

A. The U.S. Public Health Service recently reported that "a mass cytologic screening for uterine cancer is equally effective whether carried out entirely by private physician on a mail order basis or by large, public, metropolitan clinics." No matter where you are located, your patients can benefit from cytological examinations. If there is no qualified cytologist in your area, I'll gladly send you a list of laboratories that offer excellent service by mail. Write to me in care of Consultant.

Q. *Are teaching aids available for learning more about cytology?*

A. Yes, the Cancer Cytology Foundation of America provides free introductory cytology kits for the use of physicians to encourage the practice of cytodiagnosis. Write to the Cancer Cytology Foundation, 115 E. 69th Street, New York, New York, requesting the cytology kit or for technical information about cytodiagnosis.

COMPAZINE®

brand of prochlorperazine

TO STOP VOMITING

in disease-induced vomiting

'Compazine' provides prompt control of nausea and vomiting associated with such conditions as gastroenteritis, uremia, or cancer. In addition, it allays the anxiety and tension that often accompany nausea and vomiting.

in drug-induced vomiting

'Compazine' can promptly control nausea and vomiting caused by a wide range of drugs including nitrogen mustards, para-aminosalicylate and general anesthetics.

in radiation sickness

'Compazine' often stops nausea and vomiting from irradiation treatments, even when other agents have failed. Administered prophylactically, 'Compazine' often enables patients to continue irradiation therapy without interruption.

For complete prescribing information see back of magazine.

SK&F

this overweight patient is about to get the assistance she needs to stick to her prescribed diet:

Dexamyl® Spansule®

brand of sustained release capsules

- daylong control of appetite
- smooth mood improvement
- few, if any, troublesome side effects

FORMULA: Each 'Spansule' capsule No. 1 contains Dexedrine® (brand of dextro amphetamine sulfate), 10 mg.; amobarbital [Warning, may be habit forming], 1 gr. Each 'Spansule' capsule No. 2 contains 'Dexedrine' (brand of dextro amphetamine sulfate), 15 mg.; amobarbital [Warning, may be habit forming], 1½ gr. The active ingredients of the 'Spansule' capsule are distributed among hundreds of minute pellets with varying disintegration times. A therapeutic dose is released immediately and the remaining medication, released slowly and without interruption, sustains the effect for 10 to 12 hours.

INDICATIONS: (1) for control of appetite in overweight; (2) for mood elevation in mild depressive states.

USUAL DOSAGE: One 'Dexamyl' *Spansule* capsule taken in the morning.

SIDE EFFECTS: Insomnia, excitability and increased motor activity are infrequent and ordinarily mild.

CAUTIONS: Use with caution in patients hypersensitive to sympathomimetic compounds or barbiturates and in cases of coronary or cardiovascular disease or severe hypertension.

Prescribing information adopted January 1961.

SK&F *Smith Kline & French Laboratories, Philadelphia*

THORAZINE®
brand of chlorpromazine

PRESCRIBING INFORMATION

Tranquilizer • Antiemetic • Potentiator

The wide diversity of clinical applications in which 'Thorazine' is valuable, as either a specific or an adjuvant, is due to its three fundamental clinical properties: (1) its capacity to alleviate anxiety, tension and agitation without dulling mental acuity, (2) its ability to potentiate sedatives, narcotics and anesthetics, and (3) its profound antiemetic effect.

The tranquilizing effect of 'Thorazine' accounts for its usefulness in somatic conditions where emotional stress is a factor, as well as in mental and emotional disturbances *per se*.

INDICATIONS

The value of 'Thorazine' is established in the following conditions:

Moderate to severe mental and emotional disturbances of everyday practice, particularly those disturbances marked by agitation, tension, apprehension, excitement, or anxiety.

Somatic conditions complicated by emotional stress, such as arthritis, tuberculosis, severe tension headaches, gastrointestinal disorders, dermatologic conditions, status asthmaticus and severe asthma.

Hospitalized psychiatric patients, to control agitation, dispel delusions and hallucinations, and at the same time to restore or increase the patient's capacity to respond to psychotherapy.

Nausea, vomiting and hiccups, with dramatic results in severe and refractory cases.

Acute or chronic alcoholism, to control agitation, delirium tremens, and nausea and vomiting.

Cancer, as an adjuvant, to control apprehension, suffering due to pain, and nausea and vomiting.

Intractable pain, to reduce suffering and to potentiate narcotics or sedatives.

Obstetrics, as an adjuvant, to control apprehension, pain, and nausea and vomiting. 'Thorazine' allows a reduction in the amounts of the drugs ordinarily used in obstetrical management, thus lessening the risk of respiratory depression in mother and infant.

Surgery, as an adjuvant, to control anxiety and apprehension, pain, and nausea and vomiting; and to reduce by potentiation the amounts of narcotics, sedatives and anesthetics needed.

ADULT DOSAGE AND ADMINISTRATION

Dosage should always be adjusted to the response of the individual and the severity of the condition. It is important to increase dosage until symptoms are controlled or side effects become troublesome.

Mental and Emotional Disturbances of Everyday Practice – Depending on severity, *starting oral dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. After a day or two, dosage may be increased by increments of 20 mg. to 50 mg. daily, at semiweekly intervals (increase should be more gradual in emaciated or senile patients) until achieving maximum clinical response. Continue dosage at this level for at least two weeks; then it can usually be reduced to a maintenance level. A daily dosage of 200 mg. is "average," but in some cases, such as discharged mental patients, daily dosages as high as 800 mg. may be necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If necessary, and if no hypotension occurs, repeat the initial dose in one hour. Subsequent dosages should be oral, starting at 25 mg. to 50 mg. t.i.d.

Somatic Conditions Complicated by Emotional Stress–*Starting oral dosage* is 10 mg. to 25 mg. t.i.d. or q.i.d. Increase gradually by 10 mg. to 25 mg. increments at semiweekly or weekly intervals. *Starting intramuscular dosage* is 25 mg. (1 cc.), repeated after one hour if necessary and if no hypotension occurs.

Hospitalized Psychiatric Patients – ***Acutely agitated, manic, or disturbed patients:*** *Starting intramuscular dose* is 25 mg. (1 cc.). If no marked hypotension occurs, an additional 25 mg. to 50 mg. injection may be given after one hour. Subsequent intramuscular dosages may be increased gradually over a period of several days – even up to 400 mg. q4-6h in exceptionally severe cases – until the patient is controlled. (In elderly or emaciated patients the dosage should be increased more slowly than in other patients.) Usually the patient becomes quiet and cooperative within 24 to 48 hours after the initial dose, at which time oral doses may gradually be substituted for intramuscular doses (mg. for mg. or higher). Even if control is not complete, oral doses may gradually replace intramuscular doses. During this period, oral dosage should be increased rapidly until the patient is calm. Usually an *oral dose* of 500 mg. a day is sufficient but, if necessary, the dosage may be gradually increased still further to 2,000 mg. a day or higher. ***Less acutely agitated patients:*** *Starting oral dose* is 25 mg. t.i.d. Subsequently, increase the amount gradually until an effective dosage is reached – usually 400 mg. daily is sufficient. ***Duration of therapy:*** It is important to determine the optimal dosage regimen and to continue treatment long enough for maximum clinical response. Maximum improvement is sometimes not apparent until after weeks or even months of therapy.

Nausea and Vomiting – *Starting oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n., and may be increased if necessary. *Starting intramuscular dose* is 25 mg. (1 cc.). If no hypotension occurs subsequent doses of 25 mg. to 50 mg. q3-4h, p.r.n., may be given until vomiting is checked. Then replace intramuscular administration with oral. *Starting rectal dosage* is one 100 mg. suppository q6-8h, p.r.n. In some patients, one-half this dose may be sufficient.

Hiccups – *Starting oral dosage* is 25 mg. to 50 mg. t.i.d. or q.i.d. If after 2-3 days symptoms persist, *an intramuscular dosage* of 25 mg. to 50 mg. (1-2 cc.) may be used. *Use intravenous administration* only when symptoms still persist. By slow infusion, 25 mg. to 50 mg. (1-2 cc.) should be administered in 500 cc. to 1,000 cc. of physiologic saline solution, with the patient kept flat in bed. Follow blood pressure closely.

Alcoholism – ***Severely agitated patients:*** *Starting intramuscular dose* is 25 mg. to 50 mg. (1-2 cc.). Repeat initial dose if necessary and if no hypotension occurs. Start subsequent oral dosages at 25 mg. to 50 mg. t.i.d. ***Agitated but manageable patients:*** *Starting oral dose* is 50 mg., followed by 25 mg. to 50 mg. t.i.d. ***Ambulatory patients with withdrawal symptoms or sober chronic alcoholics:*** *Starting oral dose* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Patients in a stuporous condition should be allowed to sleep off some of the effects of the alcohol before 'Thorazine' is administered.

Cancer and Pain – ***Severe pain:*** *starting intramuscular dosage* is 25 mg. (1 cc.) b.i.d. or t.i.d. ***Milder pain:*** starting oral *dosage* is 10 mg. t.i.d. or q.i.d., or 25 mg. b.i.d. or t.i.d. Because 'Thorazine' potentiates their action, reduce the dosage of narcotics or sedatives to ¼ to ½ of the pre-'Thorazine' level.

Obstetrics – *Intramuscular dose* in labor and delivery is 12.5 mg. to 25 mg. (0.5-1 cc.), administered when dilation of the cervix reaches 3 to 5 centimeters or when strong labor is established. At the same time (but not mixed in the syringe with 'Thorazine'), ¼ to ½ the usual dose of a narcotic or sedative and, if desired, 0.4 mg. of scopolamine may be administered. Depending upon blood pressure, respiration and the general condition of the patient, the initial 'Thorazine' dose (alone or with reduced amounts of the other agents) may be repeated in 3 to 5 hours if necessary.

Surgery (Adults) – ***Preoperatively,*** *oral dose* is 25 mg. to 50 mg., 2 to 3 hours before the operation. *Intramuscular dose* is 12.5 mg. to 25 mg. (0.5-1 cc.), 1 to 2 hours before the operation. ***During surgery*** 'Thorazine' should be administered only if needed to control nausea and vomiting, retching, hiccups, or other acute symptoms. *Intramuscular dose* is 12.5 mg. (0.5 cc.), repeated in ½ hour if necessary and if no hypotension occurs.

Intravenous dose should be no more than 2 mg. per fractional injection, with injections at not less than 2-minute intervals. Also, it should not exceed 25 mg. 'Thorazine' should be diluted to 1 mg./cc. (1 cc. mixed with 24 cc. of physiologic saline solution). ***Postoperatively,*** *oral dosage* is 10 mg. to 25 mg. q4-6h, p.r.n. *Intramuscular dosage* is 12.5 mg. to 25 mg. (0.5-1 cc.), repeated in one hour if necessary and if no hypotension occurs.

PEDIATRIC DOSAGE AND ADMINISTRATION

Nausea and Vomiting, Behavior Disorders and Pain – *Oral dosage* is on the basis of ¼ mg./lb. of body weight q4-6h, until symptoms are controlled (i.e., for 40 lb. child—10 mg. q4-6h). Calculate 'Thorazine' Syrup dosage at 10 mg./5 cc. tsp. *Rectal dosage* is on the basis of ½ mg./lb. of body weight q6-8h, p.r.n. (i.e., for 20-30 lb. child—half of a 25 mg. suppository q6-8h). *Intramuscular dosage* is on the basis of ¼ mg./lb. of body weight q6-8h, p.r.n. In children up to 5 years (or 50 lbs.)—not over 40 mg./day. In children 5-12 years (or 50-100 lbs.)—not over 75 mg./day.

Pain—Because 'Thorazine' potentiates the action of narcotics and sedatives, reduce the dosage of these agents to ¼ to ½ of the pre-'Thorazine' level.

Behavior Disorders—In severe cases, 50-100 mg. daily has been used and, in older children, 200 mg. or more daily may be required.

Surgery (Children) – ***Preoperatively,*** dose is on the basis of ¼ mg./lb. of body weight given either orally 2 to 3 hours before the operation, or intramuscularly 1 to 2 hours before. ***During surgery,*** the dose is on the basis of ⅛ mg./lb. of body weight, repeated in ½ hour if necessary and if no hypotension occurs. The intravenous dose should be no more than 1 mg. per fractional injection, with injections at not less than 2-minute intervals. Intravenous dosage during surgery should not exceed recommended intramuscular dosage and should always be diluted to 1 mg./cc. ***Postoperatively,*** dosage is on the basis of ¼ mg./lb. of body weight, either orally q4-6h, p.r.n., or intramuscularly, a single dose repeated in one hour if necessary and if no hypotension occurs.

NOTES ON PARENTERAL ADMINISTRATION

Except for acute ambulatory cases, parenteral administration should generally be reserved for bedfast patients. Parenteral administration should always be made with the patient lying down and remaining so for at least ½ hour afterward because of possible hypotensive effects. The injection should be given *slowly, deep* into the upper outer quadrant of the buttock. If irritation and pain at the site of injection are problems, dilution of 'Thorazine' Injection with physiologic saline solution or 2% procaine solution may be helpful. Subcutaneous administration is not advisable, and care should be taken to avoid injecting undiluted 'Thorazine' Injection into a vein. Intravenous administration is recommended only for severe hiccups and surgery.

Because contact dermatitis has been reported, avoid getting the solution on hands or clothing.

SIDE EFFECTS

The drowsiness caused by 'Thorazine' may be unwanted in some patients. It is usually mild to moderate and disappears after the first or second week of therapy. If, however, drowsiness is troublesome, it can usually be controlled by lowering the dosage or by administering small amounts of dextro amphetamine.

Other side effects that have been reported occasionally are dryness of the mouth, nasal congestion, some constipation, miosis in a few patients and, very rarely, mydriasis. Mild fever (99°F.) may occur occasionally during the first days of therapy with large intramuscular doses. During 'Thorazine' therapy some patients have an increased appetite and gain weight. Usually these patients reach a plateau beyond which they do not gain further weight.

CAUTIONS

Jaundice: In the more than 14 million patients who have been treated with 'Thorazine' in the United States, the incidence of jaundice—regardless of indication, dosage, or mode of administration—has been low. Few cases have occurred in less than one week or after six weeks. Jaundice due to 'Thorazine' is of the so-called "obstructive" type; is without parenchymal damage; and is usually promptly reversible upon the withdrawal of 'Thorazine'. Because detailed liver function tests of 'Thorazine'-induced jaundice give a picture which mimics extrahepatic obstruction, exploratory laparotomy should be withheld until sufficient studies confirm extrahepatic obstruction.

Agranulocytosis: Agranulocytosis, although rare, has been reported in patients on 'Thorazine' therapy. Patients receiving 'Thorazine' should be observed regularly and asked to report at once the sudden appearance of sore throat or other signs of infection. If white blood counts and differential smears give an indication of cellular depression, the drug should be discontinued, and antibiotic and other suitable therapy should be instituted. Because most reported cases have occurred between the fourth and the tenth weeks of treatment, patients on prolonged therapy should be observed particularly during that period.

A moderate suppression of total white blood cells is sometimes observed in patients on 'Thorazine' therapy. If not accompanied by other symptoms, it is not an indication for discontinuing 'Thorazine'.

Potentiation: 'Thorazine' prolongs and intensifies the action of many central nervous system depressants, such as barbiturates and narcotics. Consequently, it is advisable to stop administration of such depressants before initiating 'Thorazine' therapy. Later the depressant agents may be reinstated, starting with low doses, and increasing according to response. Approximately ¼ to ½ the usual dosage of such agents is required when they are given in combination with 'Thorazine'. (However, 'Thorazine' does not potentiate the anticonvulsant action of barbiturates. In patients who are receiving anticonvulsants, the dosage of these agents—including barbiturates—should not be reduced if 'Thorazine' is started. Rather, 'Thorazine' should be started at a very low dosage and increased, if necessary.)

Hypotensive Effect: Postural hypotension and simple tachycardia may be noted in some patients. In these patients, momentary fainting and some dizziness are characteristic and usually occur shortly after the first parenteral dose, occasionally after a subsequent parenteral dose—very rarely after the first oral dose. In most cases, prompt recovery is spontaneous and all symptoms disappear within ½ to 2 hours with no subsequent ill effects. Occasionally, however, this hypotensive effect may be more severe and prolonged, producing a shock-like condition. In consideration of possible hypotensive effects, the patient should be kept under observation (preferably lying down) for some time after the initial parenteral dose. If, on rare occasions, hypotension does occur, it can ordinarily be controlled by placing the patient in a recumbent position with head lowered and legs raised. If it is desirable to administer a vasoconstrictor, 'Levophed' and 'Neo-Synephrine'★ are the most suitable. Other pressor agents, including epinephrine, are not recommended because phenothiazine derivatives may reverse the usual elevating action of these agents and cause a further lowering of blood pressure.

Antiemetic Effect: The physician should always bear in mind that the antiemetic effect of 'Thorazine' may mask signs of overdosage of toxic drugs and may obscure diagnosis of conditions such as intestinal obstruction and brain tumor.

Dermatological Reactions: Dermatological reactions have been reported. Most have been of a mild urticarial type, suggesting allergic origin. Some of them appear to be due to photosensitivity, and it is advisable that patients on 'Thorazine' avoid undue exposure to the summer sun.

Neuromuscular Reactions: With very large doses of 'Thorazine', as frequently used in psychiatric cases over long periods, there have been a few patients who have exhibited neuromuscu-

★'Levophed' and 'Neo-Synephrine' are the trademarks (Reg. U.S. Pat. Off.) of Winthrop Laboratories for its brands of levarterenol and phenylephrine respectively.

lar reactions (extrapyramidal symptoms) which closely resemble parkinsonism. Such symptoms are reversible and usually disappear within a short time after the dosage has been decreased or the drug withdrawn. These neuromuscular reactions can also be controlled by the concomitant administration of standard anti-parkinsonism agents.

Lactation: Moderate engorgement of the breast with lactation has been observed in female patients receiving very large doses of 'Thorazine'. This, however, is a transitory condition which disappears on reduction of dosage or withdrawal of the drug.

CONTRAINDICATIONS

In comatose states due to central nervous system depressants (alcohol, barbiturates, narcotics, etc.), and also in patients under the influence of large amounts of barbiturates or narcotics.

AVAILABLE

Tablets, 10 mg., 25 mg., 50 mg. and 100 mg., in bottles of 50, 500 and 5000; 200 mg., for use in mental hospitals, in bottles of 500 and 5000. (Each tablet contains chlorpromazine hydrochloride, 10 mg., 25 mg., 50 mg., 100 mg., or 200 mg.)

Ampuls, 1 cc. and 2 cc. (25 mg./cc.), in boxes of 6, 100 and 500. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 6 mg.)

Multiple-dose Vials, 10 cc. (25 mg./cc.), in boxes of 1, 20 and 100. (Each cc. contains, in aqueous solution, chlorpromazine hydrochloride, 25 mg.; ascorbic acid, 2 mg.; sodium bisulfite, 1 mg.; sodium sulfite, 1 mg.; sodium chloride, 1 mg. Contains benzyl alcohol, 2%, as preservative).

Spansule® capsules, 30 mg., 75 mg., 150 mg. and 200 mg., in bottles of 30, 250 and 1500; also 300 mg., in bottles of 30 and 1500. (Each 'Spansule' capsule contains chlorpromazine hydrochloride, 30 mg., 75 mg., 150 mg., 200 mg., or 300 mg.)

Syrup, 10 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. (Each 5 cc. contains chlorpromazine hydrochloride, 10 mg.)

Suppositories, 25 mg. and 100 mg., in boxes of 6. (Each suppository contains chlorpromazine, 25 mg. or 100 mg.; glycerin, glyceryl monopalmitate, glyceryl monostereate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids, lecithin.)

Concentrate (for hospital use), 30 mg./cc., in 4 fl. oz. bottles, packages of 12 and 36; and in 1 gal. bottles. (Each cc. contains chlorpromazine hydrochloride, 30 mg.)

Prescribing information adopted January, 1961

COMPAZINE®
brand of prochlorperazine

PRESCRIBING INFORMATION

Antiemetic • Tranquilizer

'Compazine' provides a beneficial calming effect and prompt antiemetic action with unusual freedom from drowsiness and depressing effect. Clinical experience in several million patients has shown 'Compazine' to be promptly effective in low dosage, with minimal side effects in the dosage range recommended for everyday practice.

INDICATIONS

*1. **Anxiety, tension, agitation,*** confusion, chronic alcoholism and behavior disorders in children.

*2. **Emotional stress associated with somatic conditions*** such as g.i. disorders, cardiovascular conditions, hypertension, menopause, premenstrual tension, neurodermatitis, arthritis, asthma, cancer, tuberculosis and tension headache.

*3. **Nausea and vomiting of widely varying causes*** such as pregnancy, postoperative conditions, viral gastroenteritis and other infectious conditions, irradiation therapy and motion sickness. In most patients, relief is provided within a short time after one oral dose.

*4. **In surgery and obstetrics*** to prevent or control: (a) nausea, vomiting and retching; and (b) fear, tension and restlessness.

*5. **In psychiatry*** to control agitation, anxiety, tension and confusion that may be seen in psychotic states.

ADMINISTRATION AND USUAL DOSAGE

Dosage should be determined according to the severity of the condition and the response of the patient. It is important to begin therapy with the lowest recommended dosage. In hospitalized patients or those under adequate supervision, higher doses may be indicated.

USUAL ADULT DOSAGE

Tablets: The usual starting dosage is 5 mg. three or four times daily. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. Dosage over 40 mg. daily should be used only in resistant cases.

Spansule® sustained release capsules: The usual starting dosage is one 15 mg. 'Spansule' capsule taken upon arising, or one 10 mg. 'Spansule' capsule in the morning and evening. Some patients may subsequently require dosage increased to one 30 mg. capsule in the morning. Dosage over 40 mg. daily should be used only in resistant cases. (B.i.d. dosage of the 30 mg. capsule should be limited to severe cases.)

Dosage recommendations for other oral forms of 'Compazine' may be applied to 'Compazine' *Spansule* capsules on the basis of the total daily dose in milligrams. (For example: one 15 mg. 'Compazine' *Spansule* capsule replaces 5 mg. 'Compazine' Tablets, t.i.d.) All strengths have the same *duration* of action. They differ only in *intensity* of therapeutic effect.

In "morning sickness" of pregnancy, one 'Compazine' *Spansule* capsule taken before retiring affords antiemetic activity throughout the night and into the morning, thus protecting against "morning sickness."

The 15 mg. 'Compazine' *Spansule* capsule is ideal for once-a-day administration. The 10 mg. 'Compazine' *Spansule* capsule is ideal for twice-a-day (q12h) administration.

Syrup: 5 mg. to 10 mg. (1 to 2 teaspoonfuls) three or four times daily.

Suppositories: Usual dosage in adults is one 25 mg. 'Compazine' Suppository twice daily.

Injection: Total parenteral dosage in 24 hours should not exceed 40 mg.

For intramuscular administration, an initial dose of 5 mg. to 10 mg. (1 to 2 cc.) of 'Compazine' Injection should be injected *deeply* into the upper outer quadrant of the buttock. Repeat, if necessary, at intervals of 3 to 4 hours. Pain at the site of injection has not been a problem. ***For intravenous administration,*** see surgery section. Dilution is not required. ***Subcutaneous administration*** is not advisable because of local irritation.

It is recommended that 'Compazine' Injection not be mixed with other agents in the syringe.

Dermatitis due to contact with 'Compazine' has not been a problem. However, it is recommended that nurses or others giving frequent injections take precautions to avoid getting the solution on their hands or clothing.

'Compazine' Injection should be protected from light, since exposure may cause discoloration. Slight yellowish discoloration will not significantly alter the potency or therapeutic efficacy. However, if markedly discolored, the solution should be discarded.

IN SURGERY (Adults)

ROUTE	DOSAGE
preoperatively	
Intramuscular injection	5 mg. to 10 mg. (1-2 cc.)

1 to 2 hours before induction of anesthesia. Repeat once in 30 minutes if necessary.

ROUTE	DOSAGE
Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

15 to 30 minutes before induction of anesthesia.

Intravenous infusion	20 mg. (4 cc.) per liter of isotonic solution

Add to I.V. infusion 15 to 30 minutes before induction. Repeat once if necessary.

during surgery

Intramuscular or Intravenous injection	5 mg. to 10 mg. (1-2 cc.)

When needed to control acute symptoms. Repeat once if necessary.

postoperatively

To prevent anxiety, nausea, vomiting, or emergence excitement, add to I.V. infusion: 20 mg. (4 cc.) per liter of isotonic solution.

For immediate control of acute nausea, vomiting, retching, or emergence excitement, inject 5 mg. to 10 mg. (1-2 cc.), I.V. or I.M. Repeat once if necessary.

IN OBSTETRICS

'Compazine' dosage should be adjusted to the individual patient and her condition in accordance with the general use of the drug (i.e., 5 mg. to 10 mg. per dose; 15 mg. to 40 mg. per day). The following dosage suggestions should prove satisfactory for the majority of obstetric patients.

To relieve anxiety or prevent vomiting during the first stage of labor, the usual dosage is 10 mg. of 'Compazine' by intramuscular injection. As labor progresses, or if it is prolonged, subsequent 10 mg. doses may be administered as needed. The total daily dose need rarely exceed 30 mg.

To control postpartum anxiety or nausea and vomiting, the usual total daily dose of 'Compazine' is 15 mg. to 30 mg. administered orally or intramuscularly.

NOTE: 'Compazine' has no clinically significant potentiating effect on narcotics, anesthetics, or sedatives. However, because the 'Compazine' patient is calm and relaxed, it is sometimes possible to produce satisfactory analgesia with less than the customary amounts of these agents. This lack of potentiating effect also minimizes the risk of intensifying or prolonging the effect of residual anesthetics and other depressant agents used in surgery or labor and delivery.

As with intravenous administration of any surgical or obstetric adjuvant, the increased possibility of hypotension should be kept in mind if 'Compazine' is administered by either intravenous injection or infusion.

USUAL CHILDREN'S DOSAGE

It is important always to use the lowest effective dosage, because as dosage is raised the possibility of side effects increases. There have been occasional cases of neuromuscular reactions (extrapyramidal symptoms) in children. These have been transitory and reversible.

Nausea and vomiting are usually controlled during the first day of therapy. Therefore more than one day's therapy is seldom necessary.

Weight	Dosage	Not to exceed
Under 20 lbs.	not recommended	
20-29 lbs.	2.5 mg. once or twice a day	7.5 mg. per day
30-39 lbs.	2.5 mg. b.i.d. or t.i.d.	10.0 mg. per day
40-85 lbs.	2.5 mg. t.i.d. or 5 mg. b.i.d.	15.0 mg. per day

For behavior disorders, dosage may be increased gradually, if necessary, within the following daily limits:

2 to 6 years of age: Total daily dose should not exceed 20 mg.
6 to 12 years of age: Total daily dose should not exceed 25 mg.

For rapid control of nausea and vomiting or behavior disorders:

Injection: For children under 12 years of age, each dose should be calculated on the basis of 0.06 mg. of 'Compazine' per pound of body weight and should be administered by deep intramuscular injection. For example, a 40-pound child would receive an injection of 2.5 mg. (0.5 cc.). Control is usually obtained with a single dose.

'COMPAZINE' IN PSYCHIATRY

'Compazine' is indicated for control of agitation, anxiety, tension and confusion that may be seen in such conditions as schizophrenias; manic-depressive states, manic phase; severe personality disorders; involutional psychoses; degenerative conditions; and senile psychoses.

ADULTS

Oral psychiatric dosage: *In relatively mild conditions,* as may be seen in private psychiatric practice or on outpatient clinics, the suggested starting dosage is 5 mg. t.i.d. or q.i.d. Some patients will respond better when subsequent dosage is raised to 10 mg. t.i.d. or q.i.d. *In moderate or severe conditions,* when patients are either hospitalized or under adequate supervision, the suggested starting dosage is 10 mg. t.i.d. or q.i.d. Dosage should be increased gradually until symptoms are controlled or side effects become bothersome. Experience has shown that when dosage is increased gradually (by small increments every two or three days) side effects either do not occur or are easily controlled.

Some patients will obtain satisfactory results on 50 mg. to 75 mg. of 'Compazine' daily. In more severe disturbances, the optimum dosage in most patients is 100 mg. to 150 mg. daily. With oral administration, response ordinarily becomes evident within a day or two. Longer periods of treatment are usually required before maximal improvement is obtained.

I.M. psychiatric dosage: For immediate control of severely disturbed adult patients, an initial dose of 10 mg. to 20 mg. (2-4 cc.) should be injected deeply into the upper outer quadrant of the buttock. If necessary, this dose should be repeated every 2 to 4 hours to gain control of the patient. Patients often respond shortly after the first injection. In resistant cases, the initial dose may be repeated hourly. More than three or four doses are seldom necessary. If, in rare cases, parenteral medication is indicated over a prolonged period, 10 mg. to 20 mg. (2-4 cc.) at 4- to 6-hour intervals is the usual dosage. Pain and irritation at the site of injection have rarely been encountered and some patients have been given the drug intramuscularly for periods of several weeks. After control is achieved by intramuscular administration, most patients can be switched to an oral form of the drug at the same dosage level or higher.

CHILDREN *(2 to 12 years)*

Oral psychiatric dosage: The suggested children's starting dosage in psychiatry is 2.5 mg. (½ teaspoonful of syrup) two or three times daily, or 5 mg. (one teaspoonful of syrup or one 5 mg. tablet) twice daily, according to body weight. During the first day, the total daily dose should not exceed 10 mg. Dosage is then increased according to the patient's response. (2.5 mg. and 5 mg. suppositories are also available.)

For ages 2 to 6, the total daily dosage usually does not exceed 20 mg. *For ages 6 to 12,* the total daily dosage usually does not exceed 25 mg. Because extrapyramidal symptoms have been reported in children as well as in adults, it is important to use the lowest effective dosage.

SIDE EFFECTS

In the dosage range recommended for everyday practice, side effects have been infrequent, transitory and usually mild. A few patients may experience a mild drowsiness when first taking 'Compazine'. There may also be occasional cases of dizziness,

skin reaction and neuromuscular reactions (extrapyramidal symptoms); rarely, hypotension.

Neuromuscular Reactions

Occasionally, neuromuscular reactions (extrapyramidal symptoms) have been observed with 'Compazine' therapy. It is important, therefore, to use the lowest effective dosage, because as dosage is raised the possibility of these reactions increases.

Motor Restlessness: A few patients on 'Compazine'—particularly those in whom dosage has been raised to higher levels—may experience a transient unpleasant stimulation or jitteriness, characterized by restlessness and insomnia. The dosage of 'Compazine' should not be increased while these side effects are present. Patients should be reassured that such effects are temporary and will disappear spontaneously. In those cases where the symptoms are particularly bothersome, reduction of dosage or the concomitant administration of a sedative may be helpful.

Dystonias: These neuromuscular reactions are seen in a significant percentage of hospitalized mental patients on high dosages. The muscles of the face and shoulder girdle may be selectively involved. Symptoms observed have included spasm of the neck muscles, extensor rigidity of back muscles, carpopedal spasm, eyes rolled back, trismus and swallowing difficulty. Despite some similarity to symptoms of serious neurologic disorders, these reactions are usually promptly reversible by temporary discontinuance of 'Compazine' therapy and administration of a sedative such as phenobarbital. The dosage and route of administration should be determined according to the severity of the symptoms. Patients should be reassured that the symptoms are transitory. Depending on the severity of the dystonia, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed. Note: It has been reported that injectable administration of Benadryl* may also be helpful.

Pseudo-parkinsonism: These neuromuscular reactions may resemble the classic parkinsonism syndrome. Treatment should include temporary discontinuance of 'Compazine' therapy and the administration of any standard anti-parkinsonism agent (see *PDR*). Patients should also be reassured that these symptoms are transitory. Depending on the severity of symptoms, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed.

CAUTIONS

Clinical experience has demonstrated that 'Compazine', a phenothiazine derivative, has a wide margin of safety and that there is little likelihood of blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

The antiemetic action of 'Compazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

'Compazine' has no clinically significant potentiating action. However, if depressant agents are used in conjunction with this drug, the possibility of an additive effect should be kept in mind.

CONTRAINDICATIONS

'Compazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

There is a dosage form of 'Compazine' for every medical need. Tablets, 5 mg. and 10 mg. and, for use in psychiatry, 25 mg., in bottles of 50, 500 and 5000. Each tablet contains 5 mg., 10 mg., or 25 mg. of prochlorperazine as the dimaleate.

'Spansule' capsules, 10 mg., 15 mg. and 30 mg., in bottles of 30, 250 and 1500; and, for use in psychiatry, 75 mg., in bottles of 30 and 1500. Each capsule contains 10 mg., 15 mg., 30 mg., or 75 mg. of prochlorperazine as the dimaleate.

Ampuls, 2 cc. (5 mg./cc.), in boxes of 6, 100 and 500. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 1 mg. sodium sulfite, 1 mg. sodium bisulfite, 8 mg. sodium phosphate and 12 mg. sodium biphosphate.

Multiple-dose Vials, 10 cc. (5 mg./cc.), in boxes of 1, 20 and 100. Each cc. contains, in aqueous solution: 5 mg. prochlorperazine as the ethanedisulfonate, 5 mg. sodium biphosphate, 12 mg. sodium tartrate, 0.9 mg. of sodium saccharin and 0.75% benzyl alcohol as preservative.

Suppositories, 2½ mg. (for young children), 5 mg. (for older children) and 25 mg. (for adults), in boxes of 6. Each suppository contains: 2½ mg., 5 mg., or 25 mg. of prochlorperazine with glycerin, glyceryl monopalmitate, glyceryl monostearate, hydrogenated cocoanut oil fatty acids, hydrogenated palm kernel oil fatty acids and lecithin.

Syrup, 5 mg./teaspoonful (5 cc.), in 4 fl. oz. bottles. Each 5 cc. contains 5 mg. of prochlorperazine as the ethanedisulfonate.

Concentrate (for hospital use), 10 mg./cc. in 4 fl. oz. bottles, cartons of 12 and 36. Each cc. contains 10 mg. of prochlorperazine as the ethanedisulfonate.

Prescribing information also available in *Compazine® Reference Manual, Physicians' Desk Reference,* or from your SK&F representative or your pharmacist.

Prescribing information adopted January 1961.

STELAZINE®

brand of trifluoperazine

PRESCRIBING INFORMATION

INDICATIONS

In general practice and in psychiatry 'Stelazine' is outstanding among tranquilizers because it relieves anxiety, agitation and tension—without sedation. Nor does it cause euphoria. 'Stelazine' is also effective in relieving anxiety either accompanying or causing somatic conditions. Where anorexia and insomnia are problems, 'Stelazine' usually produces a marked improvement in appetite and sleep patterns.

'Stelazine' provides a fast therapeutic response. On a convenient b.i.d. dosage regimen, many patients who have failed to respond to other agents, or have responded only poorly, are promptly relieved of their symptoms. With symptoms allayed, rapport with the physician is facilitated, and patients are more receptive to counselling or psychotherapy.

In hospitalized psychiatric patients 'Stelazine' produces rapid response in many diagnostic categories. These include acute and chronic schizophrenias, manic-depressive psychoses, involutional psychoses, chronic brain syndrome and mental deficiency.

'Stelazine' can combat psychotic symptoms without causing drowsiness. It can quiet hyperactive patients and activate withdrawn patients, and it has a marked beneficial effect on delusions and hallucinations.

'Stelazine' can rapidly terminate acute psychotic episodes. On the admissions service, intensive 'Stelazine' therapy often results in early discharges.

Also noteworthy is the effectiveness of 'Stelazine' in the treatment of hard-core, chronic and refractory schizophrenics. When administered to a group of such patients, it characteristically produces significant improvement in at least 30% to 40% of them.

ADMINISTRATION AND DOSAGE

Dosage of 'Stelazine' should be adjusted to the needs of the individual.

*Trademark Reg. U.S. Pat. Off.: 'Benadryl' for diphenhydramine hydrochloride, Parke-Davis.

1. Adult Dosage for Use in Everyday Practice
Usual starting dosage is 1 mg. twice daily. Optimal dosage is 1 mg. or 2 mg. twice daily. In everyday practice it is seldom necessary to exceed 4 mg. daily.

Because of the inherent long action of 'Stelazine', patients may be controlled on convenient b.i.d. administration; some patients may be maintained on once-a-day administration.

2. Adult Dosage for Use in Psychiatric Practice
oral (for office patients and outpatients with anxiety): The usual starting dosage is 1 mg. b.i.d. In some cases, a better response is achieved on 2 mg. b.i.d. In the treatment of these patients, it is seldom necessary to exceed 4 mg. a day. (Some patients with more severe disturbances, and discharged mental patients, may require higher dosages.) In some patients, maintenance dosage can be reduced to once-a-day administration.

oral (for patients who are either hospitalized or under adequate supervision): The usual starting dosage is 2 mg. to 5 mg. b.i.d. (Small or emaciated patients should always be started on the lower dosage.)

The majority of patients will show optimum response on 15 mg. or 20 mg. daily, although a few may require 40 mg. a day or more. It is important to give doses that are high enough for long enough periods of time – especially in chronic patients.

Optimum therapeutic dosage levels should be reached within two or three weeks after the start of therapy. When maximum therapeutic response is achieved, dosage may be reduced gradually to a satisfactory maintenance level.

intramuscular (for prompt control of severe symptoms): The usual dosage is 1 mg. to 2 mg. (½-1 cc.) by deep intramuscular injection q4-6h, p.r.n. More than 6 mg. within 24 hours is rarely necessary. As soon as a satisfactory response is observed, oral medication should be substituted at the same dosage level or slightly higher.

Only in very exceptional cases should intramuscular dosage exceed 10 mg. within 24 hours. Since 'Stelazine' has a relatively long duration of action, injections should not be given at intervals of less than 4 hours because of the possibility of an excessive cumulative effect.

'Stelazine' Injection has been exceptionally well tolerated; there is little, if any, pain and irritation at the site of injection.

3. Dosage for Psychotic and Mentally Defective Children
The dosages given below apply to children, ages 6 to 12, who are either hospitalized or under adequate supervision.

oral: The starting dosage is 1 mg. administered once a day or b.i.d., depending on the size of the child. Dosage may be increased gradually until symptoms are controlled or until side effects become troublesome. Both the rate and the amount of dosage increases should be carefully adjusted to the size of the child and the severity of the symptoms, and the lowest effective dosage should always be used. Once control is achieved, it is usually possible to reduce dosage to a satisfactory maintenance level.

In most cases, it is not necessary to exceed 15 mg. of 'Stelazine' daily. However, some older children with severe symptoms may require, and be able to tolerate, higher dosages.

intramuscular: There has been little experience with the use of 'Stelazine' Injection in children. However, if it is necessary to achieve rapid control of severe symptoms, 1 mg. (½ cc.) of 'Stelazine' may be administered intramuscularly once or twice a day, depending on the size of the child. Once control is achieved, usually after the first day, the oral dosage forms of 'Stelazine' should be substituted for the Injection.

SIDE EFFECTS

In the dosage range of 2-4 mg. daily, side effects from 'Stelazine' are infrequent. When they do occur, they are usually slight and transitory. Mild drowsiness occurs in a small percentage of patients; this usually disappears after a day or two of 'Stelazine' therapy. There are occasional cases of dizziness, mild skin reaction, dry mouth, insomnia and fatigue; rarely, neuromuscular reactions (extrapyramidal symptoms).

In hospitalized psychiatric patients receiving daily 'Stelazine' dosages of 10 mg. or more, clinical experience has shown that, when side effects occur, their appearance is usually restricted to the first two or three weeks of therapy. After this initial period, they appear infrequently, even in the course of prolonged therapy. Termination of 'Stelazine' therapy because of side effects is rarely necessary.

Side effects observed include dizziness, muscular weakness, extrapyramidal symptoms, anorexia, rash, lactation and blurred vision. Drowsiness has occurred, but has been transient, usually disappearing in a day or two.

Neuromuscular Reactions (extrapyramidal symptoms)
These symptoms are seen in a significant number of hospitalized mental patients receiving 'Stelazine'. They may be characterized by motor restlessness, be of the dystonic type, or they may resemble parkinsonism.

motor restlessness: Some patients may experience an initial transient period of stimulation or jitteriness, chiefly characterized by motor restlessness and sometimes insomnia. These patients should be reassured that this effect is temporary and will disappear spontaneously. The dosage of 'Stelazine' should not be increased while these side effects are present.

If this turbulent phase becomes too troublesome, the symptoms can be controlled by a reduction of dosage or the concomitant administration of phenobarbital or some other barbiturate.

dystonias: These symptoms are rare outside of mental hospitals, but they may be observed occasionally in patients who have received 'Stelazine' as a mild tranquilizer.

Symptoms may include: spasm of the neck muscles, sometimes progressing to torticollis; extensor rigidity of back muscles, sometimes progressing to opisthotonos; carpopedal spasm, trismus, swallowing difficulty, oculogyric crisis and protrusion of the tongue.

The onset of the dystonias may be sudden. A primary characteristic of these symptoms is their intermittency. They may last several minutes, disappear and then recur. There is typically no loss of consciousness and definite prodromata are usually present. Initially, these intermittent symptoms occur in a crescendo of intensity. Then as the effect of the drug wears off, the intervals between the occurrence of symptoms become longer, and the intensity of the symptoms subsides.

Despite their similarity to symptoms of serious neurological disorders, these dystonias are usually promptly reversible and need not cause undue alarm. They usually subside gradually within a few hours, and almost always within 24 to 48 hours, after the drug has been temporarily discontinued.

Treatment is symptomatic and conservative. *In mild cases,* reassurance of the patient is often sufficient therapy. Barbiturates are also useful. *In moderate cases,* barbiturates will usually bring rapid relief. The dosage and route of administration of the barbiturate used should be determined by the intensity of the symptoms and the response of the patient. *In more severe adult cases,* the administration of an anti-parkinsonism agent produces rapid, often dramatic, reversal of symptoms. Also, intravenous caffeine and sodium benzoate seems to be an effective and rapid antagonist to the dystonias. Depending on the severity of the dystonia, suitable supportive measures, such as maintaining a clear airway and adequate hydration, should be employed. *In children,* reassurance and barbiturates will usually control symptoms. Dosage and route of administration should be determined according to the intensity of symptoms and response of patient.

Note: It has been reported that injectable administration of 'Benadryl' may also be helpful in controlling dystonias.

pseudo-parkinsonism: These symptoms are extremely rare outside of mental hospitals.

Symptoms include: mask-like facies; drooling; tremors; pill-rolling motion; and shuffling gait.

Reassurance and sedation are important components of effective therapy. In the majority of cases these symptoms are readily reversible when an anti-parkinsonism agent is administered concomitantly with 'Stelazine'. Occasionally it is necessary to lower the dosage or to temporarily discontinue the drug.

CAUTIONS

Clinical experience has demonstrated that 'Stelazine', a phenothiazine derivative, has a wide range of safety and that there is little likelihood of either blood or liver toxicity. The physician should be aware, however, of their possible occurrence.

One of the results of 'Stelazine' therapy may be an increase in mental and physical activity. In some patients, this effect may not be desired. For example, although 'Stelazine' has relieved anxiety and, at the same time, anginal pain in patients with angina pectoris, a few such patients have complained of increased pain while taking 'Stelazine'. Therefore, if 'Stelazine' is used in angina patients, they should be observed carefully and, if an unfavorable response is noted, the drug should be withdrawn.

Hypotension has not been a problem, but nevertheless adequate precautions should be taken when the drug is used in patients with impaired cardiovascular systems.

The antiemetic action of 'Stelazine' may mask signs of overdosage of toxic drugs or may obscure the diagnosis of conditions such as intestinal obstruction and brain tumor.

Although 'Stelazine' has shown very little potentiating activity, caution should be observed when it is used in large doses in conjunction with sedatives or depressants.

CONTRAINDICATIONS

'Stelazine' is contraindicated in comatose or greatly depressed states due to central nervous system depressants.

AVAILABLE

Tablets, 1 mg. and 2 mg., in bottles of 50, 500 and 5000. (Each tablet contains 1 mg. or 2 mg. of trifluoperazine as the dihydrochloride.)

For psychiatric patients who are hospitalized or under close supervision:

Tablets, 5 mg. and 10 mg., in bottles of 50, 1500 and 5000. (Each tablet contains 5 mg. or 10 mg. of trifluoperazine as the dihydrochloride.)

Multiple-dose Vials, 10 cc. (2 mg./cc.), in boxes of 1 and 20. (Each cc. contains, in aqueous solution, 2 mg. of trifluoperazine as the dihydrochloride, 4.75 mg. of sodium tartrate, 11.6 mg. of sodium biphosphate, 0.3 mg. of sodium saccharin, and 0.75% of benzyl alcohol as preservative.)

Concentrate (for hospital use), 10 mg./cc., in 2 fl. oz. bottles, in cartons of 4 and 12. (Each cc. contains 10 mg. of trifluoperazine as the dihydrochloride.)

Prescribing information adopted Jan. 1961

PARNATE®

brand of tranylcypromine

PRESCRIBING INFORMATION

The physician should be familiar with the material on dosage, side effects and cautions given below before prescribing 'Parnate', and with the principles of monoamine oxidase inhibitor therapy and the side effects of this class of drugs as reported in the literature. Also, the physician should be familiar with the symptomatology of mental depressions and alternative methods of treatment to aid in the careful selection of patients for 'Parnate' therapy.

INDICATIONS AND LIMITATIONS OF USE

'Parnate' is indicated for the relief of symptoms of mental depression which may include dejected mood, self-depreciation, lowered activity levels, difficulty in making decisions, disturbed eating and sleeping patterns, and variations of these basic symptoms as described in the literature. The therapeutic utility of monoamine oxidase inhibitors is limited specifically to depressive symptoms; these drugs may aggravate some co-existing symptoms such as agitation or anxiety.

In psychiatry, 'Parnate' is indicated in the following diagnostic categories, subject to the limitation stated above: reactive and other psychoneurotic depressions, involutional melancholia, depressive phase of manic-depressive psychosis, psychotic depressive reactions. In the psychiatric treatment of severe endogenous depressions, it is impossible to predict, with presently known data, which patients will respond best to 'Parnate' and which to ECT. 'Parnate' may be indicated in some reactive depressions in which ECT is not indicated. 'Parnate' is not recommended to treat essentially normal responses to temporary situational difficulties.

Note: In depressed patients, the possibility of suicide should always be considered and adequate precautions taken. Exclusive reliance on drug therapy to prevent suicidal attempts is unwarranted, as there may be a delay in the onset of therapeutic effect or an increase in anxiety and agitation. Also, of course, some patients fail to respond to drug therapy.

CLINICAL EXPERIENCE

Extensive clinical trials with 'Parnate' have confirmed its effectiveness and versatility. As always in the evaluation of drugs for psychic disorders, some variation in efficacy has been reported.

These studies provide the following data on the effectiveness and fundamental properties of 'Parnate':

1. In 500 patients on whom complete data are available for statistical analysis, marked or moderate improvement was reported in 77% of the nonpsychotic patients. Marked improvement was reported in 40% and moderate improvement in 27% of the psychotic patients. Some investigators have pointed out that improvement in certain instances, particularly in milder cases, may have been due to spontaneous remission of symptoms.
2. Improvement is seen within 48 hours to three weeks after starting 'Parnate'; the response can be accelerated by using higher than standard initial dosages.
3. 'Parnate' acts primarily as an antidepressant rather than as a euphoriant. Patients feel essentially normal on 'Parnate' therapy.
4. 'Parnate' can facilitate psychotherapy by increasing the patient's willingness to exert mental effort and reducing symptom-centered preoccupations.
5. 'Parnate' appears to prevent relapses in some patients who have been treated initially with ECT.

DOSAGE

Dosage should be adjusted to the requirements of the individual patient. Dosage increases should be made only in increments of 10 mg. per day and ordinarily at intervals of one to three weeks. Side effects occur more often as dosage is increased.

Reduction from peak to maintenance dosage may be desirable before withdrawal. If withdrawn prematurely, original symptoms will recur. No tendency to produce rebound depressions of greater intensity has been seen with 'Parnate', although this is a theoretical possibility in patients treated at high dosages. Experimental work indicates that inhibition of monoamine oxidase persists for only a few days after withdrawal. Thus, any side effects due to this inhibition will probably recede rapidly upon withdrawal, which should be a distinct advantage of 'Parnate' therapy when the patient exhibits poor tolerance to antidepressant medication.

Because there is a striking relationship between dosage and speed of response, two dosage schedules are provided:

A. **Standard dosage.** (This schedule will not always produce prompt results, but it will hold the incidence of side effects to a minimum.)

1. Recommended starting dosage is 20 mg. per day — administered 10 mg. b.i.d. (morning and afternoon).
2. Continue this dosage for two to three weeks.
3. If no signs of a response appear, increase dosage to 30 mg. daily—20 mg. upon arising and 10 mg. in the afternoon.
4. Continue this dosage for at least a week.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced to a maintenance level.
6. Some patients will be maintained on 20 mg. per day; many will need only 10 mg. daily.
7. If dosages above 30 mg. daily are desired for use in exceptionally resistant cases, refer to the schedule of intensive dosage.

B. **Intensive dosage (for accelerated response).** (This schedule is for use in hospitalized patients or those under comparable supervision whenever a prompt effect is more desirable than a relative absence of side effects.)

1. Recommended starting dosage is 30 mg. per day. Administer 20 mg. in the morning and 10 mg. in the afternoon.
2. Continue this dosage for one week.
3. If no signs of a response appear, increase dosage gradually at intervals of several days to one week.
4. Dosages above 60 mg. per day are not advisable.
5. As soon as a satisfactory response is obtained, dosage may usually be reduced gradually to a maintenance level.
6. Some patients may be maintained on 20 mg. per day; many will need only 10 mg. daily.

Note: When ECT is being administered concurrently, 10 mg. b.i.d. can usually be given during the series, then reduced to 10 mg. daily for maintenance therapy.

SIDE EFFECTS

A. **At standard dosages.** Side effects in patients treated with standard doses of 'Parnate' are qualitatively the same as seen at higher dosages but are generally less frequent and less severe.

The patient may experience restlessness, overstimulation, or insomnia; may notice some weakness, drowsiness, episodes of dizziness, or dry mouth; or may report nausea, diarrhea, abdominal pain, or constipation. Occasionally, headaches have occurred. Symptoms of postural hypotension have been seen most commonly, but not exclusively, in patients with pre-existent hypertension; blood pressure returns to pretreatment levels rapidly upon discontinuation of the drug. Other side effects which might occur in rare instances are tachycardia, urinary retention, significant anorexia, skin rashes, edema, palpitations, blurred vision, tinnitus, chills, paresthesia, muscle spasm and tremors, impotence, sweating and possibly paradoxical hypertension.

Most of these side effects can usually be relieved by lowering the dosage or by giving suitable concomitant medication.

B. **At intensive treatment dosages.** When 'Parnate' is used for intensive treatment to control symptoms more rapidly, an increase in the incidence and severity of side effects must be anticipated.

At doses above 30 mg. daily, postural hypotension is a major side effect of 'Parnate' therapy. It affects largely the systolic readings and occurs mainly, but not exclusively, in patients with a history of hypertension. Rare instances of syncope have been seen. Dosage increases should be made more gradually in patients showing a tendency toward hypotension at the starting dose. Postural hypotension can be relieved by having the patient lie down until blood pressure returns to normal.

Other side effects which may occur are listed above under *standard dosages*. Headaches have occasionally been severe and incapacitating. Overstimulated behavior, which may include increased anxiety, agitation and manic symptoms, can be evidence of either a side effect or an excessive therapeutic action; if this occurs, reduce dosage or administer a phenothiazine tranquilizer.

CAUTIONS

Extensive clinical and laboratory work has shown that there is little likelihood of blood or liver toxicity. Since 'Parnate' is a non-hydrazine compound, it should prove to be exempt from the toxic effects on the liver thought to be due to the hydrazine moiety of some other drugs. However, severe toxic reactions have occurred with some monoamine oxidase inhibitors. Pending further clinical experience, 'Parnate' should probably not be used in patients with a history of liver disease or in those with abnormal liver function tests. Drug-induced jaundice is often difficult to differentiate from other jaundice. However, there has been sufficient clinical experience with 'Parnate' to demonstrate that, if it has any potentiality for producing jaundice, the reaction must be rare. Also, the usual precautions should be observed in patients with impaired renal function since there is a possibility of accumulative effects in such patients.

Although 'Parnate' has been used in combination with various drugs (particularly Stelazine®, brand of trifluoperazine), some monoamine oxidase inhibitors have been reported to have marked potentiating effects on certain drugs, e.g., sympathomimetics, central nervous system depressants, hypotensive agents and alcohol. Therefore, the physician should bear in mind the possibility of a lowered margin of safety when 'Parnate' is combined with potent drugs and should adjust dosage carefully. 'Parnate' should not be used in combination with imipramine. (The reaction of a patient who attempted suicide with a deliberate overdosage of 'Parnate' and imipramine was more severe than would have been predicted from the properties of either drug.)

CASES REQUIRING SPECIAL CONSIDERATION

Administer with caution to patients with recent myocardial infarction or coronary artery disease with angina of effort. Increased physical activity and, more rarely, hypotension have been reported. The pharmacologic properties of 'Parnate' suggest that it may have a capacity to suppress anginal pain that would otherwise serve as a warning sign of myocardial ischemia. When 'Parnate', like any agent which lowers blood pressure, is withdrawn from patients who tend to be hypertensive, blood pressure may again rise to undesirable levels.

When 'Parnate' is combined with a phenothiazine derivative or other compound known to affect blood pressure, elderly patients and those with cardiovascular inadequacies should be observed more closely because of the possibility of additive hypotensive effects.

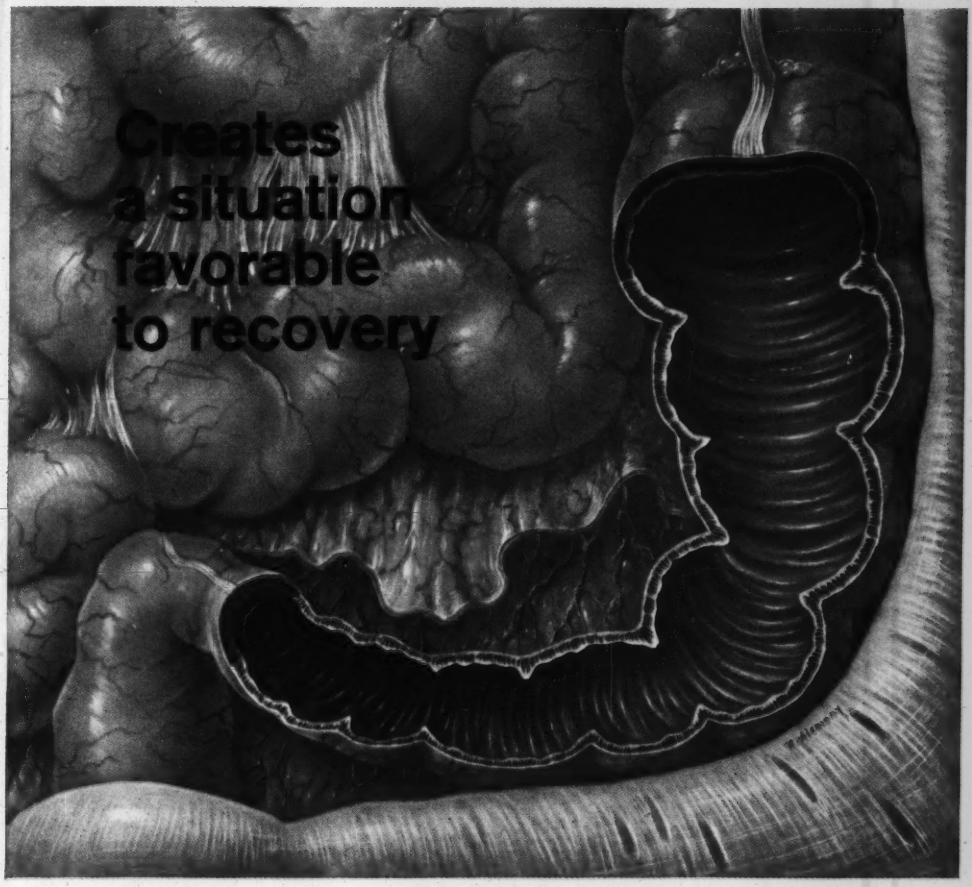
In patients being transferred to 'Parnate' from another monoamine oxidase inhibitor or from imipramine, allow a medication-free interval of one week, then initiate 'Parnate' using half the normal dosage for at least the first week of therapy. Similarly, a few days should elapse between the discontinuance of 'Parnate' and the administration of another monoamine oxidase inhibitor or of imipramine.

Because the influence of 'Parnate' on the convulsive threshold is variable in animal experiments, suitable precautions should be taken if epileptic patients are treated.

AVAILABLE

Tablets, 10 mg., in bottles of 50 and 1500. (Each tablet contains 10 mg. of tranylcypromine, as the sulfate.)

Prescribing information adopted Feb. 1961



In Spastic Colon: 'Combid' *Spansule* capsules relieve psychic as well as physical factors. Anxiety and tension—the usual causes of spastic colon—are controlled. At the same time, spasm is relieved in the colon itself.

The usual 'Combid' regimen: one dose q12h.

SK&F Combid® Spansule®

brand of sustained release capsules

PRESCRIBING INFORMATION:

'Combid' *Spansule* capsules are a logical combination of 5 mg. of Darbid® (brand of isopropamide) as the iodide, a unique, inherently long-acting anticholinergic; and 10 mg. of Compazine®(brand of prochlorperazine) as the dimaleate, the outstanding tranquilizer/antiemetic, in sustained release form.

Among the many conditions in which 'Combid' *Spansule* capsules are indicated are: peptic ulcer, hyperchlorhydria, pyloroduodenal irritability, irritable or spastic colon, gastric neurosis, gastritis, aerophagia, pyrosis, "nervous stomach," functional diarrhea, drug-induced diarrhea, mucous colitis, ulcerative colitis, genitourinary spasm, and nausea and vomiting of pregnancy.

ADMINISTRATION AND DOSAGE: One 'Combid' *Spansule* capsule b.i.d. (every 12 hours). Some patients may require only one capsule every 24 hours, on arising. Only in the exceptional patient will it be necessary to increase the dosage to two capsules b.i.d. (morning and evening).

CONTRAINDICATIONS: As is true with any preparation containing an anticholinergic, 'Combid' *Spansule* capsules should not be prescribed for patients with glaucoma, pyloric obstruction, or prostatic hypertrophy. Also, because of the antiemetic action of the 'Compazine' component (a phenothiazine derivative), 'Combid' *Spansule* capsules should not be used where nausea and vomiting are believed to be a manifestation of intestinal obstruction or brain tumor.

Clinical experience has demonstrated that 'Combid' has a wide margin of safety and that there is little likelihood of blood or liver toxicity or neuromuscular reactions (extrapyramidal symptoms). The physician should be aware, however, of their possible occurrence. When 'Combid' is used with depressant drugs, the possibility of an additive effect should be borne in mind. An occasional patient may experience mild drowsiness when first taking 'Combid'.

Prescribing information adopted January 1961.